

UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS

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IN RE BIOGEN IDEC, INC. : Civil Action  
SECURITIES LITIGATION : No. 05-10400-RCL  
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**APPENDIX OF THE PUBLICLY-AVAILABLE COMPLETE  
TRANSCRIPT OF THE MARCH 7-8, 2006 ADVISORY COMMITTEE HEARINGS**

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Dated: November 15, 2006

**DOCUMENT**

**EXHIBIT**

Peripheral and Central Nervous System Drugs Advisory Committee Hearing Transcript (3/7/06) ( <i>available at</i> <a href="http://www.fda.gov/OHRMS/DOCKETS/AC/06/transcripts/2006-4208T1.pdf">http://www.fda.gov/OHRMS/DOCKETS/AC/06/transcripts/2006-4208T1.pdf</a> ) .....	1
Peripheral and Central Nervous System Drugs Advisory Committee Hearing Transcript (3/8/06) ( <i>available at</i> <a href="http://www.fda.gov/OHRMS/DOCKETS/AC/06/transcripts/2006-4208T2.pdf">http://www.fda.gov/OHRMS/DOCKETS/AC/06/transcripts/2006-4208T2.pdf</a> ) .....	2

Dated: November 15, 2006  
Boston, Massachusetts

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I, Michael S. Hines, hereby certify that a true copy of the foregoing document filed through the ECF system will be electronically sent to the registered participants as identified on the Notice of Electronic Filing, and paper copies will be sent to those indicated as non-registered participants on November 15, 2006.

Dated: November 15, 2006

/s/ Michael S. Hines  
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# **EXHIBIT 1**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS  
ADVISORY COMMITTEE

Volume I

Tuesday, March 7, 2006

1:55 p.m.

Holiday Inn Gaithersburg  
The Ballrooms  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

PARTICIPANTS

Karl Kieburtz, M.D., M.P.H., Chair  
Sohail Mosaddegh, RPh., Pharm.D., Acting Exec. Sec.

COMMITTEE MEMBERS (VOTING)

James R. Couch, Jr., M.D., Ph.D., F.A.C.P.  
Steven T. DeKosky, M.D.  
Larry B. Goldstein, M.D.  
Michael D. Hughes, Ph.D.  
Lily K.F. Jung, M.D., M.M.M. (Consumer  
Representative)  
Ralph L. Sacco, M.D., M.S.

COMMITTEE MEMBER (Non-Voting)

Roger Porter, M.D. (Industry Representative)

TEMPORARY CONSULTANTS

Carol Koski, M.D.  
Justin C. McArthur, M.D.  
George Ricaurte, M.D., Ph.D.  
James Sejvar, M.D.  
Cynthia Sitcov (Patient Representative)

FDA PARTICIPANTS

Russell Katz, M.D.  
Marc Walton, Ph.D., M.D.  
Susan McDermott, M.D.  
Alice Hughes, M.D.  
Robert Temple, M.D.  
Gerald Dal Pan, M.D., MHS  
Douglas Throckmorton, M.D.  
Diane Wysowski, Ph.D.

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1 P R O C E E D I N G S

2 Call to Order and Introductions

3 DR. KIEBURTZ: We are going to get  
4 started, so if people would take their seats,  
5 please.

6 It may seem like a relatively long time,  
7 but we only have approximately 16 hours to do some  
8 serious deliberations here, and the bulk of today,  
9 we will be hearing from various presenters. We  
10 will hear from the sponsor, Biogen Idec, we will  
11 hear from the FDA, and we will hear from the  
12 public.

13 There is an agenda, and we will stick to  
14 the agenda. I would just like to advise all  
15 parties who are speaking that we will stick to the  
16 agenda, so please be mindful for your speakers of  
17 the time.

18 We will start the sponsor's presentation  
19 at 8:30, and that will conclude at 10:00, and the  
20 same for the FDA. Presentations will begin at  
21 10:30, and will conclude at 11:45. I am sorry if  
22 all your speakers haven't had a chance to speak by

1 that time, but that will be the end of the  
2 presentation.

3 In the afternoon, we have many comments  
4 from the public, and I would point out that there  
5 are approximately 44 public speakers registered to  
6 speak, but very few of them actually have signed  
7 in. If you are registered as a potential public  
8 speaker, please be sure you sign in at the table,  
9 so that we know you are here.

10 The time for those presentations will be  
11 tight because of the number of people. In the  
12 interest of being fair and equitable, we will keep  
13 to the scheduled time for each speaker. More about  
14 that later.

15 There are also 15 seats available outside  
16 with television monitor and audiovisual  
17 information.

18 So, it is a long day. The committee will  
19 not deliberate today, so everybody is clear on  
20 that. The committee will begin deliberations  
21 tomorrow. No matter when we finish today, the  
22 committee will not deliberate today.

1 Just one last thing for the ladies and  
2 gentlemen of the press, just bear in mind it is not  
3 appropriate for committee members to speak on the  
4 record about this meeting until after the  
5 conclusion of tomorrow. Similarly, it is not  
6 appropriate to ask them to do so, so please refrain  
7 from doing so.

8 With those preliminaries set, I would like  
9 to go around and have people introduce themselves.  
10 Maybe we will start going clockwise. After the  
11 introductions, we will have the reading of the  
12 Conflict of Interest Statement, and then we will  
13 hear from Dr. Katz.

14 DR. THROCKMORTON: I am Douglas  
15 Throckmorton. I am the Deputy Center Director in  
16 the Center for Drug Evaluation and Research.

17 DR. KATZ: I am Russ Katz, Director of the  
18 Division of Neurology Products, FDA.

19 DR. McDERMOTT: I am Susan McDermott. I  
20 am a clinical reviewer in the Division of Neurology  
21 Products.

22 DR. A. HUGHES: I am Alice Hughes. I am a

1 clinical safety reviewer in the Division of  
2 Neurology Products.

3 DR. DAL PAN: I am Gerald Dal Pan, the  
4 Director of the Office of Drug Safety at FDA.

5 DR. M. HUGHES: I am Michael Hughes. I am  
6 Professor of Biostatistics at Harvard School of  
7 Public Health.

8 DR. COUCH: I am James Couch. I am  
9 Professor of Neurology and Chair of Neurology,  
10 University of Oklahoma School of Medicine.

11 DR. MOSADDEGH: I am Sohail Mosaddegh, the  
12 Acting Executive Secretary for the Peripheral and  
13 Central Nervous System Drugs Advisory Committee.

14 DR. KIEBURTZ: I am Karl Kieburtz. I am  
15 Professor of Neurology at the University of  
16 Rochester Medical Center, and serving as the Chair  
17 of the PCNS Advisory Committee.

18 DR. McARTHUR: I am Justin McArthur. I am  
19 Professor of Neurology at Johns Hopkins University.

20 MS. SITCOV: I am Cynthia Sitcov. I am  
21 the Patient Representative. I have been diagnosed  
22 with MS for 31 years, and I did not go to medical

1 school.

2 DR. JUNG: I am Lily Jung. I am from  
3 Seattle, Washington, and I am the Consumer  
4 Representative for this committee.

5 DR. SACCO: Ralph Sacco. I am Professor  
6 of Neurology and Epidemiology from Columbia  
7 University. I am a member of the panel.

8 DR. RICAURTE: I am George Ricaurte. I am  
9 Associate Professor in the Department of Neurology  
10 at Johns Hopkins University.

11 DR. SEJVAR: Jim Sejvar. I am a  
12 neurologist and medical epidemiologist with the  
13 Centers for Disease Control.

14 DR. DeKOSKY: I am Steve DeKosky. I am  
15 the Chair of Neurology at the University of  
16 Pittsburgh.

17 DR. GOLDSTEIN: I am Larry Goldstein. I  
18 am Professor of Medicine and Director of the Stroke  
19 Center at Duke.

20 DR. KOSKI: Carol Koski, Professor of  
21 Neurology, University of Maryland School of  
22 Medicine.

1 DR. PORTER: Roger Porter, Adjunct  
2 Professor of Neurology at Penn, Adjunct Professor  
3 of Pharmacology at USUHS, non-voting pharma member.

4 DR. KIEBURTZ: Dr. Katz, is there anyone  
5 else from the FDA you want to have introduced at  
6 this point?

7 DR. KATZ: We expect a few others as you  
8 can see by the name tags, but they are not here.  
9 Marc Walton is the Deputy Director of Neurology  
10 Products, and Dr. Temple is the Director of the  
11 Office of Drug Evaluation I, who will be here  
12 shortly, one hopes.

13 DR. KIEBURTZ: Thanks.

14 Conflict of Interest Statement

15 DR. MOSADDEGH: The following announcement  
16 addresses the issue of conflict of interest and is  
17 made part of the record to preclude even the  
18 appearance of such at this meeting.

19 Based on the submitted agenda and all  
20 financial interests reported by the committee's  
21 participants, it has been determined that all  
22 interests in firms regulated by the Center for Drug

1 Evaluation and Research present no potential for an  
2 appearance of a conflict of interest at this  
3 meeting with the following exceptions.

4 In accordance with 18 U.S.C. Section  
5 208(b)(3), the following participants have been  
6 granted full waivers:

7 Dr. Steven DeKosky for unrelated  
8 consulting and speakers bureau activities for a  
9 competing firm for which he receives less than  
10 \$10,001 per year, and for unrelated activities in a  
11 visiting professor program for a university which  
12 receives support from a competing firm for which he  
13 receives less than \$10,001 per year;

14 Dr. Karl Kieburtz for consulting on  
15 unrelated matters for the sponsor and three  
16 competitors. He receives between \$10,001 and  
17 \$50,000 per year from the sponsor and less than  
18 \$10,001 per year per firm from the competitors;

19 Dr. Ralph Sacco for consulting on  
20 unrelated matters for a competitor for which he  
21 receives less than \$10,001 per year;

22 Dr. Larry Goldstein for serving on an

1 advisory board and steering committee for a  
2 competitor regarding unrelated issues for which he  
3 receives from \$10,001 to \$50,000 per year and for  
4 consulting on unrelated matters for a competitor  
5 for which he receives less than \$10,001 per year;

6 Dr. Lily Jung for serving on a speakers  
7 bureau for the sponsor for which she receives from  
8 \$10,001 to \$50,000 per year and for serving on  
9 speakers bureau for two competitors for which she  
10 receives less than \$10,001 per year per firm.

11 A copy of the waiver statements may be  
12 obtained by submitting a written request to the  
13 Agency's Freedom of Information Office, Room 12A-30  
14 of the Parklawn Building.

15 We would also like to note that Dr. Roger  
16 J. Porter has been invited to participate as an  
17 industry representative acting on behalf of  
18 regulated industry. Dr. Porter's role on this  
19 committee is to represent industry interests in  
20 general, and not any one particular company. Dr.  
21 Porter is a retired employee of Wyeth Research.

22 In the event that the discussions involve

1 any other products or firms not already on the  
2 agenda for which an FDA participant has a financial  
3 interest, the participants are aware of the need to  
4 exclude themselves from such involvement and their  
5 exclusion will be noted for the record.

6 With respect to all other participants, we  
7 ask in the interest of fairness that they address  
8 any current or previous financial involvement with  
9 any firm whose product they may wish to comment  
10 upon.

11 Thank you.

12 DR. KIEBURTZ: Any further comments from  
13 the committee on the Conflict of Interest  
14 Statement?

15 [No response.]

16 DR. KIEBURTZ: Dr. Katz.

17 Opening Remarks and Overview of Issues

18 DR. KATZ: Thanks, Dr. Kieburtz.

19 I would just like to make a very few brief  
20 opening remarks to sort of set the context for  
21 today's discussion. First, I would like to welcome  
22 the members of the PCNS Advisory Committee.

1           In particular, I would like to welcome our  
2   invited guests who have agreed to come here and  
3   help us with this very important issue, and  
4   especially I would like to thank the committee and  
5   guests for, at the very last minute, opening up  
6   their schedules, so that they could be here or you  
7   could be here for a second day, a second day that  
8   was necessitated by the intense public interest in  
9   this issue.

10           As you know, we are here to discuss the  
11   BLA for the use of Tysabri, also known as  
12   natalizumab, in the treatment of patients with  
13   relapsing-remitting multiple sclerosis.

14           Tysabri again, as you know, is a  
15   monoclonal antibody that binds to integrins on the  
16   surface of leukocytes and presumably, as a result,  
17   inhibits their migration into areas of  
18   inflammation, and presumably, this is responsible  
19   for its activity.

20           It was approved for marketing in November  
21   of 2004 on the basis of results at one year in two  
22   randomized controlled trials, Study 1801, which

1 examined the effects of Tysabri's monotherapy, in  
2 Study 1802, which examined the effects of Tysabri  
3 in conjunction with Avonex interferon beta 1a.

4 Each of these studies demonstrated  
5 clinically important effects on annualized relapse  
6 rate compared to control, and although drugs to  
7 treat MS are typically required to show effects at  
8 two years prior to approval, these effects were so  
9 robust at one year that the drug was approved on  
10 the basis of these results although the sponsor was  
11 required under the Accelerated Approval regulations  
12 of Subpart E to provide the results of two years of  
13 study after approval.

14 Unfortunately, as everyone in the room  
15 knows, in February of 2005, the sponsor informed  
16 the Agency of two cases of progressive multifocal  
17 leukoencephalopathy, or PML, a typically fatal  
18 viral infection of the brain in patients receiving  
19 Tysabri in conjunction with Avonex.

20 As a result of this, the product was  
21 withdrawn from the market in February of 2005, and  
22 the sponsor subsequently undertook an examination

1 of all their patients in their clinical trials and  
2 detected one additional case of PML in a patient  
3 with Crohn's disease.

4 The sponsor has now come back to us with  
5 the results both of their two-year clinical trials,  
6 as well as the results of their search for  
7 additional cases of PML in their patients in the  
8 clinical trials, and you will hear a great deal  
9 about the details of this over the next two days. I  
10 won't go into that.

11 The fundamental questions we bring to you  
12 are whether or not you believe these data justify  
13 the remarketing of Tysabri, and if you do, under  
14 what circumstances you believe it would be  
15 appropriate to do so, and in particular, we are  
16 interested to know whether or not you believe its  
17 use should be restricted in some way. For example,  
18 should it be reserved for patients who have failed  
19 other treatments, who have severe disease, who are  
20 not receiving other concomitant medications for MS  
21 or perhaps in any other way you might deem  
22 appropriate.

1           Importantly, the sponsor has also proposed  
2   that Tysabri be remarketed under a so-called risk  
3   minimization plan or a RiskMAP, which is a plan  
4   designed to track all patients who receive the drug  
5   with the goal of identifying, quantifying, and  
6   ideally minimizing, at least in a global sense,  
7   significant risks associated with the use of  
8   Tysabri, and if you believe that Tysabri can be  
9   remarketed under certain circumstances, we are  
10  eager to learn your views about the critical  
11  elements of such a monitoring plan, and if you have  
12  seen the revised question list, you can see that we  
13  have asked very detailed questions about the  
14  specifics of the plan. It is very important for us  
15  to know what you believe about those.

16           It is important to note that when  
17  marketing for Tysabri was suspended, all clinical  
18  trials in all indications were suspended, as well,  
19  and several weeks ago, as you probably know, we  
20  agreed with the sponsor that patients with MS, who  
21  had previously been receiving Tysabri in Phase 3  
22  studies at the time of the suspension, could once

1 again receive treatment under the IND.

2 This re-initiation of treatment under the  
3 IND is being undertaken with extensive close  
4 monitoring including neurological exams and  
5 measurement of serum JC virus, the virus that is  
6 known to cause PML, prior to each monthly infusion.

7 It is clear therefore that the Agency has  
8 decided that at least under certain circumstances,  
9 certain patients can continue to receive Tysabri at  
10 this time, but it is important to note that  
11 treatment under these intensive monitored  
12 conditions, and again which is limited to patients  
13 who have already received Tysabri and were doing  
14 well in someone's view, represents a very different  
15 scenario than the one that the sponsor now proposes  
16 for marketing.

17 It is absolutely critical to state at this  
18 point that if marketing is permitted, we fully  
19 expect that additional cases of PML, many likely to  
20 be fatal, will occur. We don't know with great  
21 confidence the true rate of PML that is associated  
22 with the use of Tysabri.

1           Although the current IND data suggest that  
2   the accrued rate, at least in MS patients, is about  
3   1 in 1,000, and we don't have detailed information  
4   about many of the factors that might affect the  
5   risk, including, but certainly not limited to,  
6   whether or not the risk is affected by the use of  
7   concomitant immunosuppressant or other treatments,  
8   and importantly, whether the risk increases with  
9   increasing duration of treatment.

10           Nonetheless, unless we can identify risk  
11   factors or tests that can reliably permit an  
12   intervention that will halt the progression or  
13   onset of PML--and I should add that we don't think  
14   such tests are available at this point--there will  
15   be additional cases of PML and perhaps many cases,  
16   and there will likely be considerable mortality  
17   associated with the use of the drug, and this is a  
18   fact that I don't believe will necessarily change  
19   based on what you hear today and tomorrow, and it  
20   is a fact that patients, their families, and  
21   prescribers will need to consider very seriously.

22           Against this somewhat unknown risk will

1 need to be considered the fact that MS is an often  
2 devastating disease for which current treatments  
3 are not always adequate, and that the treatment  
4 effect of Tysabri seems quite robust, at least  
5 certain treatment effects, and in certain respects,  
6 the treatment effect appears larger than that of  
7 available treatments, although it has to be  
8 admitted that there are no direct head-to-head  
9 comparisons in controlled trials.

10 So, it is the difficult task of weighing  
11 these risks somewhat unknown and benefits that we  
12 have brought you here today and tomorrow to  
13 discuss.

14 Let me just say a very brief word about  
15 the agenda. As you can see, and Dr. Kiebert has  
16 mentioned the agenda already, the sponsor will  
17 present the bulk of the effectiveness and safety  
18 data, and they will also present the elements of  
19 their proposed risk minimization plan.

20 Following that, the Agency reviewers will  
21 present some additional effectiveness data and  
22 raise some safety issues, as well as some issues

21

1 that we believe still exist with the proposed  
2 minimization plan.

3 Following these presentations, as you have  
4 already heard, we will have the public session in  
5 which over 40 speakers have registered to offer  
6 their views on these issues. Again, as you know,  
7 because there are so many speakers, we have asked  
8 you to come back tomorrow and have a full, complete  
9 discussion in an unrushed way tomorrow.

10 Again, I will stop there, I would like to  
11 thank the committee for coming, for the work you  
12 have already done in preparation for today's  
13 meeting, and for the work that you are about to do.

14 Thanks.

15 DR. KIEBURTZ: Does anyone on the  
16 committee have any questions for Dr. Katz?

17 [No response.]

18 DR. KIEBURTZ: Well, the good news is we  
19 are ahead of schedule.

20 The next speaker will be Dr. Adelman.

21 Sponsor Presentation

22 Biogen Idec

1 Introduction

2 DR. ADELMAN: Good morning, members of the  
3 Advisory Committee, colleagues from the Food and  
4 Drug Administration, and members of the audience.

5 My name is Burt Adelman. I am the  
6 Executive Vice President of Development at Biogen  
7 Idec.

8 [Slide.]

9 On behalf of my colleagues at Biogen Idec  
10 and Elan Pharma, I want to thank you for coming  
11 here today to consider our request to return  
12 natalizumab, Tysabri, to the short list of drugs  
13 available for the treatment of relapsing forms of  
14 multiple sclerosis.

15 [Slide.]

16 Now, natalizumab was approved for  
17 treatment of MS on November 23rd, 2004, after  
18 priority review of one year of data from two  
19 ongoing Phase III clinical trials. Prior to  
20 review, an accelerated approval recognized the  
21 strength of both efficacy and safety data at one  
22 year.

1           Approximately 7,000 patients received at  
2   least one dose within the first three months after  
3   approval. We believe that the great demand for  
4   this new product by highly informed patient and  
5   physician groups is a clear demonstration of the  
6   significant unmet need of MS patients for more and  
7   better therapies.

8           In February of 2005, within a 24-hour  
9   period, we identified one confirmed and one  
10   possible case of progressive multifocal  
11   leukoencephalopathy. This occurred in MS clinical  
12   trial patients who had received over two years of  
13   natalizumab.

14          Within a week of identifying these  
15   patients, we chose to withdraw natalizumab from the  
16   market and stop all dosing both in the market and  
17   in clinical trials. We made this decision in  
18   collaboration with the FDA.

19          Our purpose was simple. We wanted to  
20   minimize any additional risk to treated patients  
21   while we undertook an extensive investigation to  
22   understand the significance of these findings.

1           Short after natalizumab withdrawal, we  
2   convened a meeting of PML and MS experts and  
3   invited representatives of the FDA and the EMEA to  
4   join us. At this meeting, we reviewed the  
5   pathobiology of PML and its possible relationship  
6   to the effect of natalizumab.

7           Although no clear conclusions emerged, a  
8   path forward was defined. We agreed to rapidly  
9   evaluate all trial patients for clinical and  
10   radiologic evidence of PML and serologic evidence  
11   of JC virus replication in plasma and cerebral  
12   spinal fluid.

13          A protocol was devised in collaboration  
14   with these experts and regulatory authorities  
15   reviewed the protocol. In addition, colleagues at  
16   the Karolinska Institute provided matched control  
17   and treatment-naive MS patient plasma and CSF  
18   samples for JC virus testing, truly a wonderful  
19   contribution to this effort.

20          These investigations confirmed that only  
21   three patients had contracted PML. Furthermore, no  
22   evidence emerged to suggest that natalizumab

1 treatment routinely promoted JC virus replication  
2 in blood or CSF, and just as importantly, in those  
3 samples that we obtained from the Karolinska  
4 Institute, we found no evidence that  
5 treatment-naive MS patients have increased  
6 incidence of JC virus replication in the blood or  
7 CSF.

8           Although the riddle of PML is not solved,  
9 we believe that our efforts enable us to define  
10 appropriate use conditions for Tysabri while we  
11 continue to assess its risks and benefits.

12           Most individuals diagnosed with MS suffer  
13 a relentlessly progressive disease characterized by  
14 unpredictable acute exacerbations, increasing  
15 physical disability, cognitive impairment, and  
16 often secondary neuropsychiatric complications.

17           The burden and disability of multiple  
18 sclerosis is certainly similar in magnitude to that  
19 of other autoimmune diseases, such as rheumatoid  
20 arthritis, Crohn's disease, and severe psoriasis.

21           These disorders are effectively treated  
22 with highly active immunomodulatory agents. As we

1 all know, these drugs are commonly associated with  
2 serious mechanism-based toxicities including  
3 opportunistic infection and malignancy.

4 Patients and physicians have learned how  
5 to use these medicines successfully and maximize  
6 their efficacy and manage, but not eliminate, their  
7 risks.

8 We believe data you will review today  
9 clearly identify natalizumab as a highly effective  
10 treatment for MS patients. In fact, analysis of  
11 two-year data from the Phase III program has  
12 confirmed and extended the efficacy profile  
13 originally described in the label at the end of one  
14 year.

15 We now know that Tysabri can significantly  
16 reduce the risk of disability progression in  
17 addition to its sustained effect on relapse rate.

18 [Slide.]

19 We are now proposing the following usage  
20 statement for the package insert. Tysabri is  
21 indicated only for the treatment of patients with  
22 relapsing forms of multiple sclerosis to delay the

1 progression of physical disability and to reduce  
2 the frequency of clinical exacerbations.

3 We believe that Tysabri should be used as  
4 monotherapy in patients not immunocompromised.

5 Recognizing our responsibility to ensure  
6 that patients and prescribers benefit from all our  
7 current knowledge regarding risk and appropriate  
8 use conditions for natalizumab, we have designed a  
9 companion risk management and assessment program,  
10 commonly called a RiskMAP.

11 The RiskMAP plan is intended to exclude  
12 from treatment any MS patient with evidence of  
13 immune dysfunction consistent with our current  
14 hypothesis that risk of PML in Tysabri-treated  
15 patients is increased by concomitant immune  
16 compromise.

17 Further the RiskMAP establishes a  
18 comprehensive pharmacovigilance program that will  
19 enable us to proactively detect new safety signals  
20 and rapidly inform patients, physicians, and the  
21 FDA of any and all important new findings. We will  
22 present this program to you in detail today.

1           Biogen Idec and Elan Pharma are committed  
2   to a continuing effort to better understand JC  
3   virus pathobiology and PML. For example, we are  
4   examining the utility of various testing methods  
5   for JC virus in blood and blood constituents. Were  
6   any of these strategies to prove useful in early  
7   detection or in patient selection, we would include  
8   them immediately in the RiskMAP.

9           It is our intention today to ensure you  
10   that Biogen Idec and Elan, in collaboration with  
11   the FDA and prescribing neurologists, can  
12   effectively manage the use of this important new  
13   drug for the treatment of patients with MS.

14           [Slide.]

15           This is our agenda. Following me will be  
16   Dr. Alfred Sandrock, who runs our clinical  
17   development program for MS; Michael Panzara,  
18   another of our clinical neurologists, will discuss  
19   in detail the safety profile as we know it today  
20   for natalizumab. Then, Carmen Bozic, who runs our  
21   pharmacovigilance unit, will describe the RiskMAP  
22   to you.

1           We are also fortunate to have with us Dr.  
2 Rick Rudick, Director of the Mellen Center and  
3 Chairman of the Division of Clinical Research at  
4 the Cleveland Clinic Foundation, a well-known MS  
5 neurologist, who will speak to the risk-benefits of  
6 Tysabri.

7           [Slide.]

8           We are also pleased to have with us Dr.  
9 David Clifford, Professor of Neurology and Medicine  
10 at the Washington University School of Medicine in  
11 St. Louis.

12           Dr. Clifford is an eminent clinical  
13 neurologist and much of his practice is devoted to  
14 taking care of patients with AIDS and immune  
15 disorders, and the neurologic complications  
16 thereof.

17           Dr. Clifford was a member of the  
18 Independent Assessment Committee that reviewed all  
19 the patients that had been treated in the  
20 natalizumab trials, and was the senior author of  
21 the recently published IAC report in The New  
22 England Journal of Medicine.

1 Thank you very much for your time and  
2 consideration.

3 Dr. Sandrock.

4 DR. KIEBURTZ: Does anyone on the  
5 committee have any questions of clarification,  
6 ambiguity?

7 [No response.]

8 DR. KIEBURTZ: Thank you.

9 Efficacy Data

10 DR. SANDROCK: Good morning, ladies and  
11 gentlemen. My name is Al Sandrock, and I will be  
12 reviewing the efficacy of natalizumab. Before I do  
13 that, I would like to provide a brief introduction  
14 to multiple sclerosis.

15 [Slide.]

16 MS is a chronic neurological disease  
17 affecting approximately 400,000 Americans. It is a  
18 disease of young adults, mostly women, and about 85  
19 percent of patients begin with a relapsing form.

20 This form is characterized by  
21 inflammation, predominantly of the white matter.  
22 It is widely believed to have an autoimmune

1 etiology, and the consequences of this inflammation  
2 include demyelination, axonal transection, and  
3 eventually neurodegeneration.

4 [Slide.]

5 MS takes a heavy toll on patients,  
6 progression of physical disability is a common  
7 feature. Natural history studies show that the  
8 median time to requiring a cane or crutch to walk  
9 half a city block is approximately 15 years, and  
10 that the median time to requiring a wheelchair is  
11 about 25 years.

12 During the relapsing-remitting stage of  
13 the disease, unresolved relapses are a major  
14 contributor to the progression of physical  
15 disability.

16 Cognitive dysfunction is also highly  
17 prevalent, occurring in approximately 50 percent of  
18 patients. It affects employment, activities of  
19 daily living, and family and social contacts.

20 Although MS is not immediately  
21 life-threatening, it is life-shortening. Studies  
22 show a 5- to 7-year decrease in life expectancy and

1 a 2- to 7-fold increase in the risk of suicide.

2 About half of MS patients die of causes related to  
3 the disease.

4 [Slide.]

5 There are three principal outcome measures  
6 utilized in MS clinical trials: an assessment of  
7 clinical relapses, an assessment of disability  
8 progression, and MS lesions can be directly  
9 visualized by magnetic resonance imaging. I will  
10 take you through each of these in the next few  
11 slides.

12 [Slide.]

13 Relapses define MS during the  
14 relapsing-remitting stage. This green line shows a  
15 clinical course in a typical patient with a  
16 relapsing form of multiple sclerosis where  
17 disability is plotted with respect to time.

18 Relapses occur suddenly and unpredictably,  
19 and the neurologic deficits may last for weeks or  
20 months. Although patients may recover fully from  
21 relapses, about 40 percent of the time relapses  
22 result in residual disability.

1           Natural history studies have shown that  
2   relapse frequency in the early stages of the  
3   disease predicts future disability, thus, reducing  
4   the frequency of relapse is an important treatment  
5   goal in multiple sclerosis.

6           After 7 to 10 years, patients transition  
7   to the secondary progressive stage of disease where  
8   disability progression can occur gradually, even in  
9   the absence of relapse. Importantly, there are no  
10   disease-modifying therapies known today to slow the  
11   gradual progression of disability during the stage  
12   of the illness.

13           [Slide.]

14           Disability is measured in clinical trials  
15   by the use of the Expanded Disability Status Scale  
16   or EDSS. It is a 10-point scale divided into  
17   half-point increments where zero is normal and 10  
18   is death due to MS.

19           A 2-step change, which in most parts of  
20   the scale is a 1-point change, is considered  
21   clinically significant.

22           [Slide.]

1           The multiple sclerosis functional  
2    composite score, or MSFC, is an alternative scale  
3    that correlates with and supplements the EDSS. It  
4    is a composite score of ambulation, upper extremity  
5    dexterity, and cognition. In this score, lower  
6    scores indicate worsening.

7           [Slide.]

8           MS lesions begin as gadolinium-enhancing  
9    lesions, which correspond to areas of acute  
10   inflammation, as shown by the perivascular  
11   infiltrate of leukocytes in the lower left panel.

12           Although enhancing lesions are evanescent,  
13   lasting for 1 to 2 months, they leave behind a scar  
14   in the form of T2-hyperintense lesions, which  
15   therefore corresponds to the familiar MS plaques,  
16   as shown in the lower middle panel, which is a  
17   section of cerebral cortex stained brown for myelin  
18   and where the white region is the plaque.

19           Inflammation can be so intense so as to  
20   destroy brain parenchyma, and when that occurs,  
21   T1-hypointense lesions develop. Non-enhancing  
22   T1-hypointense lesions correspond to areas of

1 axonal transection, as shown in the lower right  
2 panel, which is a high-power view in MS lesions  
3 stained green for neurofilament and where the  
4 arrows point to transected axons.

5 [Slide.]

6 Two general classes of disease-modifying  
7 therapies have been approved for the treatment of  
8 relapsing forms of multiple sclerosis in the United  
9 States - interferon-beta and glatiramer acetate.

10 There are three forms of interferon-beta,  
11 and they reduce the rate of relapse relative to  
12 placebo by approximately one-third. They also  
13 reduce the progression of physical disability as  
14 measured by the EDSS, the portion progressing at  
15 two years, also by approximately one-third.

16 These drugs result in injection site  
17 reactions or flu-like symptoms which are common  
18 adverse events. Depression has also been  
19 associated with interferon use, and there are rare  
20 cases of liver failure.

21 Glatiramer acetate also reduces the  
22 frequency of relapses by approximately one-third,

1 and the Phase III trial of this agent failed to  
2 show a significant effect on disability  
3 progression.

4 Because it requires daily subcutaneous  
5 injections, injection site reactions are common.  
6 Lipoatrophy and acute systemic reactions are also  
7 seen.

8 [Slide.]

9 An unmet need remains in MS because these  
10 agents are partially effective. The Phase III  
11 trials of these agents show that most patients  
12 experience disability progression while on the  
13 drug. About two-thirds of patients will have at  
14 least one relapse within two years of starting  
15 therapy, and about a quarter of patients worsen by  
16 at least 1 point on the EDSS scale within two years  
17 of treatment initiation.

18 Not surprisingly, adherence to therapy is  
19 poor. Fifteen to 20 percent of patients discontinue  
20 their therapy annually, and there is a cohort of  
21 about 50,000 patients in this country who have  
22 attempted one or more of these therapies, but have

1 quit and have chosen to remain untreated.

2 [Slide.]

3 In order to address the unmet need in  
4 multiple sclerosis, Biogen Idec and Elan sought to  
5 develop new therapies for MS, and as we did so, we  
6 were mindful of the fact that inflammation occurs  
7 early in the course of the disease.

8 Our therapeutic hypothesis, therefore, was  
9 that if we could suppress inflammation during the  
10 early stages of MS, we could significantly alter  
11 the course of multiple sclerosis.

12 [Slide.]

13 The biology of inflammation has been  
14 clarified over the past 15 or 20 years. An  
15 important early step is the adhesion of leukocytes  
16 to the endothelial cell wall of blood vessels, and  
17 this adhesion allows for the subsequent  
18 trans-endothelial migration of these leukocytes  
19 into inflamed tissue.

20 The molecular interaction of alpha-4  
21 integrins, which are expressed on the surface of  
22 leukocytes, with cell adhesion molecules, such as

1 VCAM, which is expressed on the surface of  
2 endothelial cells, is an important molecular event  
3 that allows for the firm adhesion of leukocytes to  
4 endothelial cells.

5 [Slide.]

6 Natalizumab is a humanized monoclonal  
7 antibody directed against the alpha-4 chain of both  
8 alpha-4, beta 1, and alpha-4, beta 7 integrins.

9 By binding to the alpha-4 chain, it  
10 interferes with the alpha-4 interaction with cell  
11 adhesion molecules, thereby inhibiting the adhesion  
12 of leukocytes to endothelial cells, and inhibiting  
13 the migration of leukocytes into inflamed tissue.

14 Natalizumab has been studied in nearly  
15 5,000 patients in the total clinical experience, of  
16 which about 3,000 were on natalizumab. The  
17 majority of patients were in the multiple sclerosis  
18 trials, about 2,700 patients, and 2,000 of these  
19 patients were in the Phase III program, and for the  
20 remainder of my talk, I am going to focus on the  
21 data derived from those 2,000 patients in the Phase  
22 III program.

1           As Dr. Panzara comes up to speak about  
2   safety, he will also include data from the Crohn's  
3   disease and RA programs.

4           [Slide.]

5           There were two, Phase III trials of  
6   natalizumab in multiple sclerosis. The first trial  
7   was a monotherapy trial, Study 1801, which was a  
8   randomized, double-blind trial enrolling largely  
9   treatment-naive relapsing-remitting MS patients.

10          The patients were in the EDSS range of  
11   zero to 5. All patients had to have at least 1  
12   release in the year prior to entry. Patients were  
13   randomized to receive either natalizumab or placebo  
14   in a 2:1 fashion. 942 patients were enrolled in  
15   this trial.

16          The second trial was an add-on study,  
17   1802. This was also randomized and double-blinded.  
18   It also enrolled relapsing-remitting MS patients,  
19   but this time the patients had to have disease  
20   activity while on interferon. The same EDSS range  
21   was used, and patients also had to have a relapse  
22   in the year prior to entry, this time on

1 interferon.

2 Patients continued their interferon and  
3 added either natalizumab or placebo in a 1:1  
4 fashion. 1,171 patients enrolled in this trial.

5 [Slide.]

6 The study design was similar between these  
7 two trials. After a brief screening period,  
8 patients were randomized to either natalizumab 300  
9 mg I.V. once monthly or placebo I.V. once monthly,  
10 and they were followed for 120 weeks, at which time  
11 they were able to roll over into an open label  
12 safety extension study of natalizumab.

13 Throughout the treatment period, clinical  
14 evaluations, as denoted by the C's, were done every  
15 3 months, and MRI's were done at baseline and  
16 annually. There were two sets of primary  
17 endpoints, one at one year, and one at two years,  
18 at the end of the trial.

19 The primary endpoint at one year was the  
20 annualized relapse rate, and there were a number of  
21 secondary endpoints. At two years, the primary  
22 endpoint was EDSS progression, and there were also

1 a number of secondary endpoints. I will take you  
2 through each of these primary and second endpoints  
3 at both time points in the subsequent slides.

4 [Slide.]

5 I am going to focus on the data from the  
6 monotherapy trial because, as Dr. Adelman pointed  
7 out, we believe that natalizumab should be used as  
8 monotherapy.

9 [Slide.]

10 First, the annualized relapse rate. This  
11 was the primary endpoint at one year. Natalizumab  
12 led to a 68 percent reduction in the rate of  
13 relapse over that first year. We confirmed this  
14 effect at the end of the study, so that at the end  
15 of the study, there was 68 percent reduction in the  
16 frequency of relapses.

17 [Slide.]

18 We examined the risk of relapse by looking  
19 at the cumulative probability of having a relapse  
20 over the two-year period. These are Kaplan-Meier  
21 plots of the cumulative probability of relapse.

22 The hazard ratio indicates a 60 percent

1 reduction in the risk of relapse over the two-year  
2 time period. At the one-year mark, 60 percent of  
3 placebo patients were free of relapse compared to  
4 80 percent of natalizumab-treated patients.

5 [Slide.]

6 Time to EDSS progression was the primary  
7 endpoint at two years. Here, we are looking at the  
8 cumulative probability of progressing over the  
9 two-year period where progression was defined as a  
10 two-step increase in the EDSS sustained for at  
11 least three months.

12 At the end of the two-year period, 29  
13 percent of placebo patients had progressed compared  
14 to 17 percent of natalizumab-treated patients. The  
15 hazard ratio indicates a 42 percent reduction in  
16 the risk of progressing over the two-year period.

17 [Slide.]

18 The Multiple Sclerosis Functional  
19 Composite score indicated that natalizumab-treated  
20 patients either had no change or perhaps a slight  
21 increase in the score, which denotes improvement,  
22 whereas, placebo patients worsened.

1           If we break the composite score down into  
2   its three components, natalizumab showed a benefit  
3   in all three components of ambulation, upper  
4   extremity dexterity, and cognition.

5           [Slide.]

6           Turning now to the MRI endpoints, the  
7   number of enhancing lesions provides an estimate of  
8   the inflammation going on in the brain at the time  
9   of the MRI scan.

10          On the one-year scan, there was a 92  
11   percent reduction in the mean number of enhancing  
12   lesions, and the same result was observed on the  
13   Year 2 scan.

14          [Slide.]

15          The number of new or enlarging T2 lesions  
16   provides an estimate of the accumulation of MS  
17   plaques over the time period studied. In the first  
18   year, there was an 80 percent reduction in the mean  
19   number of new or enlarging T2 lesions. Over the  
20   two-year period, there was a similar reduction, 83  
21   percent in the mean number of new or enlarging T2  
22   lesions.

1 [Slide.]

2 This slide shows the distribution of the  
3 number of new or enlarging T2 lesions over two  
4 years. If we look at the placebo group, which are  
5 the white bars, distribution is skewed toward the  
6 right, so that 68 percent of placebo patients had  
7 at least three new or enlarging T2 lesions over the  
8 two-year period.

9 In contrast, the blue bars indicate the  
10 natalizumab group, which shows that the  
11 distribution is skewed toward the left, so that 57  
12 percent of natalizumab-treated patients had no new  
13 or enlarging T2 lesions over the two-year time  
14 period.

15 [Slide.]

16 T2 lesion volume is an estimate of the  
17 total burden of disease in the brain, and the  
18 change in T2 lesion volume is shown on this slide.

19 Over the first year, there was a decrease  
20 in the volume in the natalizumab group of  
21 approximately 1,300 cubic millimeters compared to  
22 an increase of 741 cubic millimeters in the placebo

1 group.

2 A similar finding was shown over the full  
3 two-year study period, a decrease of 900 cubic  
4 millimeters compared to an increase of nearly 3,000  
5 cubic millimeters in the placebo group.

6 [Slide.]

7 The number of new T1-hypointense lesions  
8 is shown here. The mean number shows a 74 percent  
9 reduction in the mean number with natalizumab  
10 compared to placebo over the first year, and a  
11 similar finding was seen looking over the entire  
12 two-year study period, a 76 percent reduction in  
13 the mean number of new T1-hypointense lesions.

14 [Slide.]

15 We wondered whether the efficacy of  
16 natalizumab was restricted to certain subgroups, so  
17 we predefined a number of subgroups to look at.

18 This slide shows the relapse rate ratio  
19 where the vertical blue line indicates a rate ratio  
20 of 1, and points left to the 1 indicate a treatment  
21 effect in favor of natalizumab.

22 Regardless of age, gender, disability

1 status at baseline, the relapse number in the year  
2 prior to entry, presence or absence of enhancing  
3 lesions at baseline, and less than or more than 9  
4 T2 lesions at baseline, natalizumab appears to  
5 provide a favorable benefit.

6 The only group in which the confidence  
7 intervals overlap with 1 is a very small subgroup,  
8 the number of patients in the less than 9 category  
9 is quite small.

10 [Slide.]

11 Turning now briefly to the 1802 add-on  
12 study, this study summarizes all of the clinical  
13 measures of all the primary and secondary endpoints  
14 of both the 1- and 2-year mark on the clinical  
15 measures.

16 First, in terms of the relapse rate, there  
17 was 53 to 55 percent reduction in the annualized  
18 relapse rate over interferon alone. There was a  
19 decrease in EDSS progression, so that the risk was  
20 decreased by 24 percent over the time period over  
21 interferon alone.

22 The risk of relapse was decreased by 50

1 percent over interferon alone, and the MSFC also  
2 showed a favorable benefit of combination therapy  
3 compared to interferon monotherapy.

4 [Slide.]

5 This slide shows all of the MRI measures  
6 employed as secondary endpoints in the 1802 study.  
7 The drug had a substantial effect on all the MRI  
8 measures that we looked at.

9 [Slide.]

10 So, in summary, efficacy was demonstrated  
11 on all primary and secondary endpoints at both the  
12 one- and two-year marks in both Phase III trials of  
13 multiple sclerosis.

14 The magnitude of efficacy as monotherapy  
15 is compelling.

16 The add-on study confirmed efficacy in  
17 patients breaking through active treatment.

18 There was strong attenuation of  
19 inflammation and accumulation of plaque burden as  
20 seen on MRI scans, and the benefit was seen  
21 consistently across subgroups.

22 At this time, I would like to introduce

1 Dr. Michael Panzara, who will present the safety of  
2 natalizumab.

3 Safety Data

4 DR. PANZARA: Good morning, ladies and  
5 gentlemen. I am Dr. Michael Panzara, and I will  
6 review for you today the safety of natalizumab.

7 [Slide.]

8 This slide provides an outline of my  
9 presentation. As has been discussed, natalizumab  
10 was approved in November of 2004 for the treatment  
11 of relapsing forms of multiple sclerosis based on  
12 one-year data from the two ongoing Phase III  
13 studies.

14 The studies are now complete and an  
15 analysis of the safety database has yielded no  
16 appreciable differences in most adverse events as  
17 compared with the time of initial approval.

18 Therefore, I will only briefly review the  
19 general safety of natalizumab. The details of  
20 these analyses are in your briefing document, and I  
21 am pleased to answer any questions that you may  
22 have about them.

1           The one thing that has changed since the  
2 time of initial approval is infection. Therefore,  
3 the bulk of my presentation will focus on a review  
4 of the many analyses undertaken to evaluate the  
5 risk of infection in natalizumab-treated patients.

6           The final portion of my presentation will  
7 focus on progressive multifocal  
8 leukoencephalopathy, or PML, and the extensive  
9 safety evaluations undertaken following  
10 identification of PML in natalizumab-treated  
11 patients.

12           [Slide.]

13           Most of my presentation will focus on the  
14 placebo-controlled MS experience. This included  
15 1,617 patients who received natalizumab and 1,135  
16 who received placebo. There were also patients who  
17 received natalizumab in open-label studies  
18 amounting to over 2,300 MS patients and 3,800  
19 patient years of exposure.

20           I will also call upon the experience in  
21 Crohn's disease in which an additional 1,600  
22 patients received natalizumab, amounting to 1,700

1 person years of exposure, and there were some  
2 differences in the safety profile in this  
3 population, which I will indicate throughout my  
4 presentation.

5 All together, in the combined experience,  
6 nearly 4,000 patients received natalizumab and  
7 5,500 person years of exposure. In addition, there  
8 was a small rheumatoid arthritis experience, which  
9 I will also speak of during my presentation.

10 [Slide.]

11 This slide provides a general overview of  
12 the adverse events that occurred in the  
13 double-blind, placebo-controlled trials of multiple  
14 sclerosis.

15 Focusing on the first line, common adverse  
16 events were balanced between the groups.  
17 Similarly, serious adverse events were balanced,  
18 and, indeed, there were more serious adverse events  
19 on placebo than on natalizumab. This is reflective  
20 of more serious MS relapses in the placebo group as  
21 compared with natalizumab.

22 Moving to the next line, when these

1 serious adverse events are removed, the MS-related  
2 ones, the groups remained balanced.

3           Serious hypersensitivity reactions did  
4 occur on natalizumab treatment at an incidence of  
5 0.8 percent. This is the same incidence that was  
6 seen at the time of initial approval, and, indeed,  
7 there were no serious hypersensitivity reactions  
8 during the second year of the trial.

9           Moving to malignancies, 1.3 percent of  
10 placebo-treated patients had a malignancy versus  
11 0.7 percent of those on natalizumab.

12           There were three deaths on placebo versus  
13 2 on natalizumab. The deaths on natalizumab are  
14 summarized on the next slide.

15           [Slide.]

16           The first patient was a patient who had a  
17 history of malignant melanoma, who noticed a new  
18 lesion at the time of his first or second infusion,  
19 and the diagnosis was finally made after his fifth  
20 infusion.

21           The next was a patient who had received 25  
22 infusions of natalizumab, but died of alcohol

1     intoxication.

2                     [Slide.]

3                     In addition, there were four deaths that  
4     occurred in the open-label MS experience. The  
5     first was one of the cases of PML that I will  
6     describe in detail for you later in my  
7     presentation.

8                     There was one case each of a respiratory  
9     distress in a pediatric MS patient, a patient who  
10    had a seizure and arrhythmia, and one patient  
11    suicide. Each of these last three events occurred  
12    at least five months after their last natalizumab  
13    infusion.

14                    [Slide.]

15                    Turning to the Crohn's disease experience,  
16    there were six deaths that occurred in Crohn's  
17    disease clinical trials, both the  
18    placebo-controlled trials and the open-label  
19    trials.

20                    The first was a patient who died of a  
21    work-related asphyxiation. The second was a  
22    65-year-old man with a history of hypertension who

1 died of a myocardial infarction. The third was a  
2 patient who developed peritonitis as a  
3 postoperative complication of a Crohn's related  
4 procedure.

5           The next three events were serious  
6 opportunistic infections. The first was the one  
7 case of PML in a Crohn's disease patient. The next  
8 was a patient who developed pneumocystis carinii  
9 pneumonia, and the third was a patient who  
10 developed pulmonary aspergillosis. I will describe  
11 each of these last three events in detail during my  
12 discussion of opportunistic infections.

13           [Slide.]

14           Finally, there were two deaths in  
15 natalizumab-treated patients in the rheumatoid  
16 arthritis experience. The first was in a patient  
17 who developed a renal stone and then developed E.  
18 coli urosepsis that in the process of placing a  
19 central line for antibiotic treatment, developed an  
20 intraoperative pulmonary hemorrhage.

21           The final case was a woman with rheumatoid  
22 lung, which was diagnosed on autopsy.

1           So, these slides summarize the total  
2   number of deaths that occurred on natalizumab  
3   treatment in the clinical development program.

4           [Slide.]

5           Now, I would like to turn to a discussion  
6   of infections.

7           [Slide.]

8           I would like to begin by providing an  
9   overview of the many analyses undertaken to  
10   evaluate the risk of infection in  
11   natalizumab-treated patients. This will include a  
12   discussion of common infections, as well as those  
13   reported as serious.

14          Then, I will review the risk of infection  
15   over time, in other words, were there an increasing  
16   number of infections with increasing natalizumab  
17   exposure.

18          Then, I will discuss an analysis of herpes  
19   infections. This is a relatively common viral  
20   infection that we chose to study to evaluate  
21   potential effects of natalizumab on cell-mediated  
22   immunity.

1 Finally, I will review opportunistic  
2 infections including PML.

3 [Slide.]

4 This slide shows the common infections  
5 that occurred in the placebo-controlled trials of  
6 multiple sclerosis, that occurred at an incidence  
7 of 1 percent or greater than placebo on natalizumab  
8 treatment.

9 Focusing on the first line, 74 percent of  
10 patients in each group experienced an infection.  
11 There were five infections that occurred more  
12 frequently on natalizumab than placebo using this  
13 low threshold of 1 percent.

14 The types of infections that developed are  
15 quite typical of those seen in this population.  
16 Similar to the incidence, the rate of infection was  
17 balanced at 1.5 per person year in each group.

18 [Slide.]

19 This slide shows the serious infections  
20 that occurred in the placebo-controlled trials of  
21 multiple sclerosis. The infections on this slide  
22 are those that occurred at an incidence of 0.1

1 percent or greater in the natalizumab group.

2           The most common serious infections were  
3    appendicitis, urinary tract infections, and  
4    pneumonia with a maximal difference between the  
5    groups of 0.1 percent.

6           On the middle of the slide, you can see  
7    there were three reports of what was deemed a  
8    serious viral infection. Each of these were  
9    patients who developed nausea, vomiting, and fever.  
10   The viral infection resolved spontaneously or with  
11   hydration. All patients recovered and continued in  
12   the study.

13           [Slide.]

14           Now, I would like to summarize the  
15   post-marketing natalizumab experience for  
16   infections. Approximately 7,000 patients received  
17   one or more natalizumab infusions in the three  
18   months that the drug was on the U.S. market.

19           Serious infections were reported in 16  
20   patients, yielding reporting incidence of 0.2  
21   percent. Pneumonia and urinary tract infections  
22   were the most common infections reported.

1           There were two reports of serious herpes  
2   infections that occurred in the post-marketing  
3   period. The first was a case of fatal herpes  
4   encephalitis that occurred three months following a  
5   single natalizumab infusion.

6           The second was a case of herpes simplex  
7   meningitis that occurred within hours of a single  
8   natalizumab infusion. This patient recovered fully.

9           There were no opportunistic infections  
10   reported during this time including no reported  
11   cases of PML.

12           [Slide.]

13           Now, turning to the risk of infection over  
14   time. We set out to determine whether with  
15   increasing natalizumab exposure, there would be an  
16   increased risk of infection.

17           This slide is again from the double-blind,  
18   placebo-controlled trials of multiple sclerosis.  
19   The y axis shows the cumulative probability of an  
20   infection, and the x axis shows the number of weeks  
21   in the trial.

22           The Kaplan-Meier curves are nearly

1 superimposable. This indicates an equal risk of  
2 infection over the 120-week dosing interval.  
3 Likewise, the hazard ratio was 1, supporting this  
4 conclusion.

5 Thus, with increasing natalizumab  
6 exposure, there does not appear to be an increased  
7 risk of infection.

8 [Slide.]

9 Now, turning to herpes infections. As I  
10 indicated, we chose to study herpes viral  
11 infections as a marker of potential effects of  
12 natalizumab on cell-mediated immunity.

13 These are latent DNA viruses in which  
14 reactivation leads to the clinical manifestations  
15 of disease, and these viruses have a particular  
16 tropism for the nervous system. The high rate of  
17 sporadic infection in these viruses makes it  
18 amenable to study in the clinical trial setting.

19 [Slide.]

20 This table shows the incidence and rate of  
21 herpes infections that occurred in the  
22 placebo-controlled trials of multiple sclerosis.

1 Infections included in this table are  
2 those reported as herpes simplex, herpes zoster,  
3 cytomegalovirus, Epstein-Barr virus, or any  
4 infection deemed as herpetic by the investigator.

5 7.2 percent of patients on natalizumab  
6 experienced a herpes infection versus 6.1 percent  
7 of those on placebo.

8 We chose to explore this further by  
9 evaluating the incidence and rate of herpetic  
10 infections in the monotherapy study, as well as  
11 those in the combination study, and that is shown  
12 on this slide.

13 [Slide.]

14 First, focusing on the monotherapy, 6  
15 percent of patients on placebo versus 6.4 percent  
16 of those on natalizumab experienced a herpetic  
17 infection, and the rate was also balanced between  
18 the groups.

19 In contrast, in combination therapy, 6.1  
20 percent of those on placebo or Avonex alone  
21 experienced a herpetic infection as opposed to 8.4  
22 percent of those on natalizumab, and this is

1 reflected in the rate of 50 per 1,000 person years  
2 versus 67 per 1,000 person years.

3 So, this suggests that although there may  
4 be an increased risk of herpes infections that are  
5 slight, it appears to be greater in those receiving  
6 combination therapy.

7 So, to summarize, there was a slight  
8 increase in herpes infections of 1.1 percent in  
9 natalizumab-treated patients. It appears that this  
10 occurred primarily with combination treatment.  
11 There are no serious or disseminated herpes  
12 infections in the multiple sclerosis trials. There  
13 were the two cases of herpes infections in the  
14 post-marketing experience that I already described  
15 for you.

16 Although I didn't just show it, it is in  
17 your briefing document that this observation in  
18 Crohn's disease was similar. There was an increase  
19 of 0.5 percent on natalizumab-treated patients as  
20 compared with placebo.

21 Five of these events were reported as  
22 serious in the Crohn's disease trials. Two of the

1 five had onset prior to the initiation of  
2 natalizumab treatment, and all patients recovered  
3 when appropriate treatment was initiated.

4 [Slide.]

5 Now, I would like to turn to a discussion  
6 of opportunistic infections.

7 [Slide.]

8 PML did occur in natalizumab-treated  
9 patients. There were a total of three confirmed  
10 cases of PML. Two of these were in MS patients,  
11 one of these was fatal. Both patients were  
12 receiving interferon-beta concurrently at the time  
13 of diagnosis.

14 There was also one patient with PML in the  
15 Crohn's disease studies which was also fatal. This  
16 patient was originally diagnosed as having an  
17 astrocytoma, but later, a re-review of the  
18 pathology by an independent neuropathologist  
19 determined that the diagnosis was actually PML.  
20 This patient had pre-existing lymphopenia due to  
21 chronic immunosuppression use.

22 The exposure of natalizumab in these

1 patients ranged from 8 to 37 infusions and all of  
2 these patients presented with behavioral changes.

3 [Slide.]

4 This table shows the incidence of  
5 opportunistic infections in the placebo-controlled  
6 experience, as well as the cumulative MS experience  
7 for natalizumab.

8 Focusing on the righthand side of the  
9 slide, in the blue shaded area, there were a total  
10 of three patients who developed opportunistic  
11 infections on natalizumab, yielding a rate of 0.8  
12 per 1,000 person years. Two of these were the  
13 cases of PML that I have just described.

14 The only other opportunistic infection was  
15 a patient who developed a cryptosporidial  
16 gastroenteritis after 16 natalizumab infusions.  
17 This patient recovered fully.

18 Thus, other than PML, there was only one  
19 opportunistic infection in the MS experience.

20 [Slide.]

21 Turning to Crohn's disease, this slide  
22 shows the incidence of opportunistic infections in

1 the placebo-controlled and cumulative experience in  
2 Crohn's disease.

3           Again, focusing on the righthand portion  
4 of the slide, there were five events that were  
5 characterized as opportunistic in patients in the  
6 Crohn's disease studies, yielding a rate of 2.9 per  
7 1,000 person years. The details of these cases are  
8 shown in the next slide.

9           [Slide.]

10           Starting at the top of the slide, the  
11 first was the one PML case that I have already  
12 described. The next two cases I have mentioned  
13 when I reviewed the deaths on the natalizumab  
14 treatment.

15           The first was a 69-year-old man who  
16 developed pneumocystis carinii pneumonia following  
17 34 natalizumab infusions in the setting of chronic  
18 cirrhosis.

19           The next patient was a 63-year-old man who  
20 developed pulmonary aspergillosis after a prolonged  
21 hospitalization that resulted from a GI bleed in  
22 the setting of chronic prednisolone and

1 nonsteroidal use.

2           The next patient is a 33-year-old woman  
3 who developed CMV colitis following a single  
4 natalizumab infusion in the setting of  
5 azathioprine. This patient recovered  
6 spontaneously.

7           The final case was a 65-year-old woman who  
8 developed a mycobacterium avium intracellulare  
9 pneumonia following eight natalizumab infusions in  
10 the setting of chronic prednisone use, in the  
11 setting of staph aureus pneumonia. This patient  
12 also recovered fully with treatment.

13           The next three events on the slide are not  
14 considered opportunistic, but are somewhat atypical  
15 and are considered for completeness.

16           The first is a 32-year-old man who  
17 developed a lung abscess following 13 infusions of  
18 natalizumab in the setting of azathioprine. This  
19 patient recovered fully with antibiotic treatment.

20           The next is a 62-year-old woman who  
21 developed Burkholderia cepacia pneumonia, also  
22 known as pseudomonas cepacia pneumonia, following

1 three natalizumab infusions in the setting of  
2 tobacco use and congestive heart failure. This  
3 patient also recovered fully.

4 Finally, there is a 20-year-old man who  
5 developed what is presumed to be tuberculosis  
6 following 25 natalizumab infusions in the setting  
7 of prednisone and azathioprine use. This developed  
8 six months following his last natalizumab infusion.  
9 Although the diagnosis has not been confirmed  
10 either by PCR or by culture, the patient remains on  
11 tuberculosis treatment.

12 [Slide.]

13 So, to summarize, natalizumab treatment is  
14 associated with an increased risk of PML. The  
15 incidence estimate is 1 in 1,000 with broad  
16 confidence intervals ranging from 0.2 per 1,000 to  
17 2.8 per 1,000.

18 There may also be an increased risk of  
19 other opportunistic infections. There was one  
20 non-PML infection in MS patients. This is the  
21 cryptosporidial diarrhea.

22 The remaining infections occurred in

1 Crohn's disease patient with pre-existing  
2 comorbidity and immunocompromise. This may be  
3 reflective of any of these factors, and, indeed,  
4 there was a slight increase in infection in general  
5 in Crohn's disease patients.

6 [Slide.]

7 So, to summarize the safety of  
8 natalizumab, adverse events and serious adverse  
9 events were balanced between the groups. The  
10 hypersensitivity rate of 0.8 percent was consistent  
11 with the approved labeling and there was no  
12 increase in malignancy on natalizumab treatment.

13 There was no increase in the incidence or  
14 rate of common or serious infections.

15 There may be a slight increase in herpes  
16 infections on natalizumab treatment, and this  
17 appears to be more prevalent in the combination  
18 patients.

19 PML and other opportunistic infections did  
20 occur on natalizumab treatment, and these were seen  
21 mostly in Crohn's disease patients with significant  
22 comorbidity or the use of immunomodulators or

1 immunosuppressants.

2 [Slide.]

3 Now, I would like to summarize PML.

4 [Slide.]

5 First, PML is a rare, progressive  
6 infection of the central nervous system. It is  
7 often fatal within six months of diagnosis.

8 It is a lytic infection of  
9 oligodendrocytes caused by the JC virus, which is a  
10 human polyomavirus.

11 It is known to primarily affect  
12 immunocompromised individuals and was first  
13 described in the setting of hematological  
14 malignancies. It gained more prominence during the  
15 era of HIV infections, and most recently it has  
16 been described in the setting of organ  
17 transplantation.

18 [Slide.]

19 The cause of PML is the JC virus. This is  
20 a double-stranded DNA virus that is believed to  
21 infect the majority of individuals at an early age.  
22 However, the reported seroprevalence ranges from 30

1 to 80 percent depending on the assays employed.

2 The sites of latency of the JC virus  
3 include the kidney, the bone marrow, and lymphoid  
4 tissues.

5 The pathogenesis of PML is really not  
6 known, however, it likely involves a multi-step  
7 process that involves the activation of the virus  
8 from latency, a step of DNA rearrangement,  
9 interactions with the immune system, and eventual  
10 migration of the virus from sites of latency into  
11 the central nervous system.

12 [Slide.]

13 The diagnosis of PML is based on a triad  
14 of clinical, MRI, and laboratory findings. First,  
15 clinically, it is characterized by a subacute onset  
16 of progressive neurological changes. The symptoms  
17 typically localize to the subcortical region, but  
18 may also involve cerebellum.

19 On MRI, the lesions are T2-hyperintense  
20 and are typically non-enhancing without mass  
21 effect, and typically localized to the subcortical  
22 region as do the symptoms.

1           Diagnosis requires confirmation of the  
2   presence of JC virus in the central nervous system,  
3   and this is done commonly now through the use of  
4   PCR analysis of the spinal fluid looking for DNA  
5   from the JC virus.

6           Although there are no pathognomonic  
7   differences for multiple sclerosis, there are  
8   features that help one differentiate between the  
9   two.

10          First, in terms of the clinical  
11   presentation, the tempo is different. While PML  
12   symptoms typically are subacute, those of MS are  
13   typically more acute, evolving over hours to days.  
14   Likewise, the location of the lesions are somewhat  
15   different.

16          MS typically affects optic nerve or spinal  
17   cord, although can affect other areas, while these  
18   areas are almost never involved in the setting of  
19   PML, particularly the optic nerve and spinal cord.

20          On MRI, although T2 lesions develop in MS,  
21   they are typically associated with  
22   gadolinium-enhancement, edema or mass effect, and

1 are more typically periventricular.

2 In addition, JC viral DNA is not detected  
3 in the spinal fluid of MS patients.

4 There are currently no proven means for  
5 monitoring or predicting PML onset. A variety of  
6 methods have been explored. This includes serum,  
7 plasma, buffy coat, in white cells and urine. None  
8 of these have proven to be predictive or  
9 diagnostic.

10 [Slide.]

11 Unfortunately, there are no antiviral  
12 treatments for PML. It appears based on the  
13 literature that immune reconstitution may be the  
14 most effective treatment.

15 This comes from two lines of evidence.  
16 First, is the HIV experience with highly active  
17 antiretroviral treatments, or HAART. The  
18 literature shows that the introduction of HAART, at  
19 the time of diagnosis reduces the mortality of PML  
20 by half.

21 In addition, this literature has suggested  
22 that mild symptoms at treatment initiation, so

1 early in the disease, is associated with an  
2 improved prognosis.

3           The second line of evidence stems from  
4 transplantation. This literature has suggested  
5 that a reduction of immunosuppression at the time  
6 of clinical presentation of PML can improve  
7 survival, and survival is reported in one-third of  
8 patients in case series, although the experience is  
9 small.

10           The data suggest that early recognition  
11 and immune reconstitution may improve outcome.

12           [Slide.]

13           Now, I would like to review the extensive  
14 safety evaluations undertaken following  
15 identification of PML in natalizumab-treated  
16 patients.

17           [Slide.]

18           Following the suspension of dosing on the  
19 28th of February, we evaluated the patients from  
20 the clinical trials of multiple sclerosis, Crohn's  
21 disease, and rheumatoid arthritis.

22           The objectives of these evaluations were

1 3-fold. First, to determine if additional patients  
2 had undiagnosed PML or other atypical infections.  
3 Next, to determine the true prevalence of JC viral  
4 DNA in the CSF of MS patients. There was a small  
5 literature that said that JC viral DNA can be  
6 detected in up to 10 percent of MS patients. We  
7 set out to determine if this was correct.

8 Finally, we set out to assess the utility  
9 of plasma testing as a predictive test for PML.

10 [Slide.]

11 All patients were required to see their  
12 neurologist as soon as possible following dose  
13 suspension for a clinical evaluation and MRI.

14 We encouraged CSF collection for all  
15 patients, but it was required for anyone for which  
16 there was suspicion of PML.

17 We also collected plasma for exploratory  
18 analyses, and we are fortunate to have CSF and  
19 plasma control samples from the Karolinska  
20 Institute. These were from patients who were naive  
21 to treatment and those who had other neurological  
22 diseases.

1           The entire study was done in collaboration  
2   with the NIH and was monitored by an independent  
3   Adjudication Committee of experts in virology,  
4   neuroradiology, and the neurology of HIV. The role  
5   of this committee was to determine whether there  
6   are new cases of PML.

7           [Slide.]

8           Now, to the results.

9           [Slide.]

10          3,826 patients were eligible for  
11   evaluation. Ninety-one percent of the  
12   natalizumab-treated patients participated in this  
13   assessment. We had very extensive follow-up even  
14   on those who did not participate, and vital status  
15   was confirmed in over 99 percent.

16          Following this detailed analysis, there  
17   were no new cases of PML.

18          [Slide.]

19          Now, in addition to determining there were  
20   no cases of PML, we learned a great deal about PML  
21   diagnosis and monitoring.

22          First, regarding MRI, we had approximately

1 3,000 MRI scans that were reviewed by our central  
2 reader centers. We found that MRI scan was very  
3 useful to exclude the diagnosis of PML in the  
4 setting of clinical change, in the setting of  
5 patients with clinical symptoms.

6 We found that a single MRI scan was  
7 usually sufficient to rule out the diagnosis,  
8 although if there were ambiguous lesions, re-scan  
9 was sometimes required.

10 When the MRI was nondiagnostic, spinal  
11 fluid analysis was required. We found during this  
12 analysis that baseline brain MRI was very important  
13 to facilitate this assessment.

14 [Slide.]

15 We analyzed nearly 800 spinal fluid  
16 samples for the presence of JC viral DNA; 400 of  
17 these were from natalizumab-treated patients. An  
18 additional 400 were the neurological controls from  
19 the Karolinska Institute.

20 Following these analyses, no JC viral DNA  
21 was detected in either natalizumab-treated patients  
22 and those who had never seen the drug.

1           We also had spinal fluid samples from the  
2   two MS patients who had developed PML, and JC virus  
3   was detected in the spinal fluid of those two  
4   patients. Thus, this data confirms that CSF  
5   testing is very specific for the diagnosis of PML.

6           [Slide.]

7           Finally, turning to the plasma analyses,  
8   plasma was collected from 2,370 patients as an  
9   exploratory analysis. Five of these patients were  
10   found to have detectable JC viral DNA in their  
11   plasma, or 0.2 percent.

12          There were no clinical or radiographical  
13   changes associated with this finding, and, indeed,  
14   three of these patients had never received  
15   natalizumab.

16          We also re-analyzed stored serum samples  
17   from the three PML patients. JC viral DNA was not  
18   detected in two of three of these prior to symptom  
19   onset. The one patient with Crohn's disease had JC  
20   virus detected about a month before clinical  
21   symptoms.

22          So, this suggests the presence of JC virus

1 or viremia is not necessarily associated with PML,  
2 but the absence of JC virus does not exclude the  
3 diagnosis.

4 [Slide.]

5 So, in closing, although there are no  
6 proven ways to monitor for PML, there are a few  
7 options that we can consider. These options extend  
8 from the extensive evaluations over the past year,  
9 opinions from consultants, and the existing  
10 literature.

11 We believe that clinical vigilance by the  
12 neurologists is the most important means of  
13 screening. In addition, we believe that the  
14 monthly interaction between healthcare provider and  
15 patients at the time of infusion affords a unique  
16 opportunity to enhance this vigilance through the  
17 introduction of questionnaires or checklists that  
18 have a sufficiently low threshold to prompt  
19 additional evaluations by the physician.

20 The three patients who developed PML in  
21 our experience each presented with clinical signs  
22 early in the course of the disease that were

1 recognized by the patient, physician, or family  
2 members.

3 Previously, such changes would have been  
4 viewed changes secondary to multiple sclerosis  
5 rather than a rare disease like PML. Now, with  
6 what we know, any clinical change on natalizumab  
7 will be viewed as PML until proven otherwise,  
8 prompting a rapid dose suspension and additional  
9 assessments.

10 Turning to JC viral DNA in the plasma, we  
11 were hopeful about this, however, the sensitivity  
12 and predictive value appear to be unclear. Given  
13 the presence of virus in patients without PML, and  
14 the lack of patients with PML, what the results of  
15 this test suggest are not clear. Therefore, we do  
16 not believe we can recommend widescale use at this  
17 time.

18 Regarding MRI, we found MRI to be quite  
19 sensitive in the setting of new changes, but not  
20 specific in MS, but helpful diagnostically.  
21 However, given the time course of PML, which is  
22 relatively short, we could think of no practical

1 scanning frequency which would allow its use as an  
2 effective screening tool.

3 Finally, regarding spinal fluid, we found  
4 spinal fluid to be very specific at the time of  
5 diagnosis, however, the literature suggests that  
6 spinal fluid tends to be negative in early disease,  
7 even in the setting of clinical changes in MRI.  
8 This, and the fact that this is an invasive test,  
9 make it a poor screening tool.

10 So, these are the factors that we  
11 considered when designing the risk management plan  
12 that Dr. Bozic will now present to you.

13 Thank you.

14 DR. KIEBURTZ: Any questions,  
15 clarifications from the committee? Dr. McArthur.

16 DR. McARTHUR: Thank you for your  
17 presentation.

18 I had a question about the performance  
19 characteristics of the spinal fluid JCV-PCR. You  
20 have talked about the very low rate, well, the zero  
21 rate of positivity. What about positive controls  
22 from biopsy-proven PML cases, either HIV-positive

1 or not?

2 DR. PANZARA: These assays were run at the  
3 NIH using a Gene Majors method, which has a  
4 detection of 50 nanograms or 50 copies, I should  
5 say, per ml. So, it was the most sensitive assay  
6 available, and positive controls were used.  
7 Indeed, it was the same assay in which we detected  
8 JC virus in the spinal fluid of the confirmed  
9 cases.

10 DR. McARTHUR: Were the positive controls  
11 re-run in this assay, or were they essentially  
12 historical controls?

13 DR. PANZARA: No, they were positive  
14 controls run at the time of the assay, at the time  
15 of testing of these samples.

16 DR. KIEBURTZ: Dr. Jung.

17 DR. JUNG: I have a number of questions.

18 DR. KIEBURTZ: Just now clarifications,  
19 misunderstandings, misheards. General questions,  
20 we will get to. I just don't want to interrupt the  
21 sponsor too much.

22 DR. JUNG: Headaches were mentioned as

1 occurring in 35 percent of patients receiving  
2 Tysabri as opposed to 30 percent. Was there any  
3 concern that the presentation of headaches might  
4 serve as a precursor for HSV?

5 DR. PANZARA: Headache was the most common  
6 infusion-related reaction. We characterized any  
7 event that occurred within two hours of infusion as  
8 an infusion reaction. Headache was the most common  
9 event reported. It was usually reported early in  
10 the course of treatment, and then decreased over  
11 time, but it was no precursor to an infection. The  
12 patients, the vast majority continued in the trial.

13 DR. RICAURTE: Just following up on the  
14 issue of spinal fluid, did you address the question  
15 about high specificity in that sensitivity may be  
16 compromised particularly early on? I wondered if  
17 you could say a few more words about the extent of  
18 that and how that might or might not have  
19 influenced the evaluation of all of the cases for  
20 possible PML.

21 DR. PANZARA: So, there is a sensitivity  
22 of the spinal fluid. Well, the levels of DNA that

1 are detectable by this method, according to all our  
2 experts, is that which would be considered  
3 clinically relevant. Indeed, there was nothing  
4 detected below this very low threshold. So, we are  
5 very confident that this assay, if there was JC  
6 virus there, we would detect it.

7 DR. KIEBURTZ: Can I ask one last  
8 question? When you were on your slide about  
9 clinical, my attention lapsed for a moment when you  
10 said under clinical vigilance, if there is any  
11 clinical deterioration--what did you say?

12 DR. PANZARA: So, currently, our  
13 recommendation is clinical vigilance, and the risk  
14 management program that Dr. Bozic will describe, we  
15 will go through the steps that should be taken  
16 following the identification of clinical change,  
17 but basically, any clinical change should prompt an  
18 evaluation by a physician and which may include  
19 additional workup.

20 DR. KIEBURTZ: Thanks.

21 Dr. Katz.

22 DR. KATZ: I had a question for Dr.

1 Sandrock and I think a question or two for Dr.

2 Panzara, if that's okay.

3           The first question has to do with the  
4 efficacy data. You presented the data for relapse  
5 rate or annualized relapse rate by baseline EDSS.  
6 Do you have a presentation of the accumulation of  
7 disability results by baseline EDSS as opposed to  
8 just the relapse rate outcome?

9           DR. SANDROCK: Yes, I believe it's 2-9,  
10 display 2-9 in the briefing document that we  
11 provided. That provides the hazard ratio on  
12 subgroups and it is broken down in the same levels  
13 that we broke them down for the relapse rate ratio,  
14 2-10, in fact.

15           May I have Slide 2-16, please. Actually,  
16 could I have displayed 2-10.

17           [Slide.]

18           So, this is the hazard ratio in the  
19 various subgroups. In the third set, there are the  
20 hazard ratios based on the EDSS level zero to 1.5,  
21 2 to 2.5, 3 to 3.5, and greater than and equal to  
22 4.

1 DR. KIEBURTZ: You had some follow-up?

2 DR. KATZ: Yes. For either one who has  
3 the exposure data, what is the exposure, or do you  
4 have a slide for the exposure? I think you had  
5 total person years and that sort of thing, but the  
6 exposure for two years and three years, how many MS  
7 patients have gotten the drug for two years, how  
8 many have gotten it for three years?

9 DR. PANZARA: I would direct you to  
10 display 3-1 in your briefing document, but I do  
11 have a slide of that. That would be Slide 2-18.

12 [Slide.]

13 I direct your attention to the top portion  
14 of the table where we have number exposed to  
15 natalizumab. I would like you to focus your  
16 attention to the righthand side of the slide where  
17 you can see approximately 1,400 patients have  
18 received natalizumab for two or more years,  
19 approximately 150 patients have received  
20 natalizumab for three or more years. The bulk of  
21 that was in multiple sclerosis.

22 DR. KATZ: So, in MS, 1,100 patients--

1 DR. PANZARA: 1,121.

2 DR. KATZ: Exposed for two years.

3 DR. PANZARA: Two years, and 111 for three  
4 or more years.

5 DR. KATZ: Okay. And the two cases of PML  
6 occurred at two years or greater?

7 DR. PANZARA: Yes, one patient had  
8 received 29 natalizumab infusions, and one had  
9 received 37.

10 DR. KATZ: The other question I had, had  
11 to do with vital status. You said that you had  
12 vital status for greater than 99 percent of the  
13 patients, even though 91 percent participated in  
14 the follow-up study.

15 Could you just talk a little bit more  
16 about that? What do you mean by "vital status,"  
17 just alive or dead, or do you have cause of death,  
18 if there were deaths?

19 DR. PANZARA: There were no deaths. The  
20 deaths that I described to you initially in my  
21 presentation are some of those patients, you know,  
22 they weren't eligible clearly. So, we had a total

1 of about 437 patients who chose not to participate  
2 or did not participate in the assessment.

3           There were a variety of reasons for that.  
4 The most common reason was most had received  
5 placebo. We had a large number of patients who  
6 received placebo, had never received natalizumab,  
7 and really didn't feel the need to come in and have  
8 this assessment.

9           We had about another third of the patients  
10 actively decline participation, so they had to sign  
11 that they didn't want to participate, so their  
12 vital status was confirmed. A variety of other  
13 sites, who didn't want to participate, but the  
14 physician said no PML here, but I am not  
15 participating, so there were several of those.

16           There were a few cases, about 60 who were  
17 considered as quote, unquote, "lost to follow-up."  
18 We actually went to each of their physicians and  
19 had those physicians make contact with them, and we  
20 found all patients except for 10.

21           DR. KIEBURTZ: Dr. Couch.

22           DR. COUCH: Yes, just one question about

1 the MRI scan. The MRI scan is obviously one of the  
2 good ways of trying to confirm the diagnosis.

3 Is this an appropriate way of trying to  
4 look for early diagnosis through your IAC? Were  
5 you able to find that there were any ways in using  
6 the MRI scan to try to determine early diagnosis,  
7 so the immune system could be reconstituted early?

8 DR. PANZARA: The requirement was that  
9 everybody undergo an MRI scan, and what we found is  
10 that if there was any patient who had clinical  
11 symptoms that the physician was unsure of, that  
12 could be MS, could be PML, they had the MRI scan  
13 done. They referred both the MRI scan and the  
14 clinical exam to our independent Adjudication  
15 Committee.

16 The expert neuroradiologist on that  
17 committee and clinicians reviewed the history, and  
18 then made recommendation. In some cases, if the  
19 MRI was ambiguous, to go on to an additional MRI,  
20 approximately one to two months later, or a spinal  
21 tap. That was the diagnostic algorithm.

22 So, if there was any concern, they

1 underwent, first, MRI. If there was still concern,  
2 additional MRI and spinal tap was performed. We  
3 saw no signs on the scans that were reviewed. We  
4 were actively looking for the immune reconstitution  
5 syndrome, and we did not see any scans that would  
6 be suggestive of that.

7 DR. KIEBURTZ: I know the committee has  
8 further questions, but I am going to hold and let  
9 the sponsor finish their presentations, please, and  
10 we will credit you five minutes for our intervening  
11 questions.

12 Risk Management Plan

13 DR. BOZIC: Good morning, ladies and  
14 gentlemen. My name is Carmen Bozic and I am the  
15 head of Drug Safety and Risk Management at Biogen  
16 Idec.

17 So far this morning, you have heard this  
18 Dr. Sandrock and Dr. Panzara present on the  
19 efficacy and safety of natalizumab. In this  
20 presentation, I will focus on how we propose to  
21 minimize the risk of PML and also what we plan to  
22 do in order to better understand that risk.

1 [Slide.]

2 This is an outline of my presentation.

3 After I conclude with the risk management plan, I  
4 will present our perspectives on the benefit-risk  
5 profile of Tysabri.

6 [Slide.]

7 So, the Tysabri risk management plan was  
8 developed based on FDA's guidance document on this  
9 topic and based on our ongoing dialogue with the  
10 FDA.

11 I would like to point out that the plan  
12 that I will be presenting you today is an updated  
13 version of the plan that you have in your briefing  
14 document and represents an evolution in our  
15 thinking and in consideration of several  
16 discussions that we have had with the FDA on this  
17 topic.

18 In developing this plan, we carefully  
19 reviewed other existing risk management plans to  
20 gain insights into the best approach for Tysabri.

21 We found that the approach to risk  
22 management for drugs with serious risks can vary.

1 For example, clozapine, which is used for severe  
2 schizophrenia, and has a risk of agranular cytolysis,  
3 has a mandatory registry of all prescribing  
4 physicians and all treated patients.

5 On the other hand, mitoxantrone, which  
6 many of you are familiar with, and which is  
7 indicated for progressive relapsing MS, and has a  
8 risk of cardiotoxicity and acute myelogenous  
9 leukemia, does not have a mandatory registry, and  
10 while it has recommended monitoring of white cell  
11 counts and cardiac functions, these are not  
12 compulsory.

13 [Slide.]

14 Finally, and importantly, in developing  
15 this plan, we sought extensive feedback from  
16 neurologists, infusion nurses, and MS patients. We  
17 spoke to over 200 neurologists to review all the  
18 safety findings and to get their input on how best  
19 to minimize the risk of PML.

20 We also surveyed 225 patients and more  
21 than 100 infusion nurses, and sites regarding the  
22 feasibility of our proposal. We had the advantage

1 of over 10 years of experience providing for the  
2 needs of the MS community, and we understand the  
3 complexities of the setting in which MS care is  
4 delivered.

5 So, we considered the range of healthcare  
6 practices and diverse locales in which MS patients  
7 are treated from academic medical centers to  
8 private practice clinics in both urban and in rural  
9 settings where proximity to healthcare providers is  
10 a major factor to consider.

11 Thus, the plan seeks to minimize the risk  
12 of PML, but without creating unintended  
13 consequences that may obstruct patient access to  
14 Tysabri.

15 [Slide.]

16 So, our risk management plan has two sets  
17 of goals, risk minimization goals and risk  
18 assessment goals.

19 With respect to risk minimization, we want  
20 to promote informed benefit-risk decisions  
21 regarding the use of Tysabri in patients with  
22 relapsing MS. We also want to minimize the risk of

1 PML to the extent that this is possible based on  
2 currently available data, and although data on this  
3 are limited, we seek to potentially minimize death  
4 and disability if PML occurs.

5 With respect to risk assessment, we want  
6 to define more precisely the incidence and risk  
7 factors for PML in Tysabri-treated patients, and we  
8 want to assess the long-term safety of Tysabri in  
9 the clinical practice setting.

10 An important point that I want to make on  
11 this slide is that these two activities, risk  
12 minimization and risk assessment, will go on in  
13 parallel, and the data that we collect from our  
14 risk assessment activities will inform our risk  
15 minimization activities over time.

16 So, we will be continuously evaluating the  
17 risk management plan and make refinements to the  
18 plan, as appropriate, in order to achieve these  
19 goals.

20 [Slide.]

21 Now, I am going to talk about the risk  
22 minimization component of our plan.

1 [Slide.]

2 In designing our risk minimization  
3 program, we took into consideration some very  
4 important features about how MS patients are  
5 treated and how Tysabri is administered.

6 First, Tysabri has a unique mode of  
7 administration that is unlike any other drug with  
8 risk management plans.

9 It is administered monthly by infusion in  
10 the infusion center setting under the care and  
11 supervision of a healthcare professional,  
12 typically, an infusion nurse. This affords a  
13 monthly opportunity to reinforce the risk of PML  
14 with the patient and to screen the patient for  
15 potentially new neurological symptoms that might be  
16 indicative of PML.

17 Secondly, the care of MS patients is  
18 highly specialized. We know that approximately  
19 6,000 neurologists take care of over 90 percent of  
20 MS patients in this country. What this means is we  
21 can reach virtually all prescribers and teach them  
22 about PML and about the diagnosis of PML if it

1 occurs.

2 Finally, neurologists, because PML is a  
3 disease of the central nervous system, it stands to  
4 reason that the neurologists are the best qualified  
5 specialists to diagnose and manage PML if it  
6 occurs, and it also means that they will have the  
7 expertise to apply the educational tools that we  
8 will give them about the diagnosis and management  
9 of PML.

10 [Slide.]

11 Now, I will talk about the revised  
12 labeling for Tysabri and then I will describe the  
13 risk minimization system that we are proposing to  
14 support the revised labeling.

15 [Slide.]

16 The new revised labeling for Tysabri will  
17 feature a prominent boxed warning. We are  
18 recommending the use of the box, because this is  
19 the highest level warning we can put into a drug  
20 label.

21 In the box, we are stating that Tysabri is  
22 associated with an increased risk of PML which

1 causes death or severe disability.

2 We are also actively warning against  
3 concurrent use of Tysabri with immunosuppressants,  
4 such as azathioprine, or immunomodulators, such as  
5 beta-interferon.

6 We are stating in the box that Tysabri is  
7 indicated only for the treatment of patient with  
8 relapsing MS, because it is only in those patients  
9 that the benefit has been proven.

10 Finally, we are highlighting the  
11 importance of clinical vigilance as a means for  
12 possibly early detection of PML, and we are  
13 instructing healthcare professionals to be alert to  
14 any signs or symptoms that might be suggestive of  
15 PML, and if they find such symptoms, they should  
16 immediately suspend dosing of Tysabri and begin an  
17 evaluation, which would include a brain MRI, as  
18 well as CSF testing for JC viral DNA.

19 [Slide.]

20 We are also including additional warnings  
21 and contraindications in the labeling. We are  
22 stating that an MRI scan should be performed prior

1 to initiating Tysabri, because it may be helpful in  
2 differentiating PML from MS symptoms in the patient  
3 with new neurological symptoms.

4 We are also contraindicating the use of  
5 Tysabri in patients who are immunocompromised,  
6 including patients who are immunocompromised due to  
7 underlying diseases, such as HIV, hematological  
8 malignancies or transplantation, or patients who  
9 are immunocompromised due to prior  
10 immunosuppressant therapies.

11 [Slide.]

12 Now, I will talk about our risk  
13 minimization system.

14 [Slide.]

15 A key feature of our program is that we  
16 will require mandatory enrollment of all  
17 prescribers and all Tysabri-treated patients into a  
18 registry, called the Tysabri Registry. All  
19 prescribing physicians and patients must complete  
20 and sign a mandatory enrollment form and send it to  
21 Biogen Idec before initiating Tysabri therapy.

22 We also have a new controlled centralized

1 distribution system that will allow us to know the  
2 location and number of all Tysabri vials that we  
3 are shipping, and we will allow Tysabri to be used  
4 and administered only in registered infusion  
5 centers.

6           These are infusion centers that have been  
7 trained on the appropriate use of Tysabri and the  
8 risks and benefits of Tysabri, and which have  
9 attested that they will comply with the risk  
10 management requirements.

11           With this system, we can deliver  
12 educational tools to all neurologists who are  
13 prescribing Tysabri, all nurses who are  
14 administering Tysabri, and all Tysabri-treated MS  
15 patients.

16           In the next few slides, I will cover in  
17 more detail the specific elements of our system.

18           [Slide.]

19           A key component of the enrollment form is  
20 a patient-physician acknowledgment. This records  
21 that an informed benefit-risk decision has taken  
22 place before the start of therapy.

1           On this form, the physicians will sign  
2   that they are aware that PML is a risk with Tysabri  
3   treatment and it can cause death or severe  
4   disability, that they have discussed the risks and  
5   benefits of Tysabri with their patient including  
6   the risk of PML, and that they are prescribing  
7   Tysabri for a patient who is appropriate for  
8   Tysabri. This is a patient with relapsing MS, not  
9   in combination with any immunosuppressant or  
10   immunomodulators, and not in a patient who is  
11   immunocompromised.

12           On this acknowledgment, the patients will  
13   sign that they have read the Medication Guide, they  
14   have discussed the risks and benefits of Tysabri  
15   with their physician, including the risk of PML,  
16   and that they will report any new or worsening  
17   neurological symptoms to their physician.

18           The signed patient-physician  
19   acknowledgment on the enrollment form must be sent  
20   to Biogen Idec as a prerequisite to starting  
21   Tysabri treatment.

22           Now, I will speak about the requirements

1 that we have imposed on infusion centers.

2 [Slide.]

3 As I said before, Tysabri can be used only  
4 in registered infusion centers. These are centers  
5 that have received educational training from our  
6 personnel and have attested that they will follow  
7 the risk management requirements.

8 These requirements are that they can dose  
9 only patients who have been enrolled in the Tysabri  
10 Registry, they must give a Medication Guide to  
11 every patient before every dose, they must document  
12 this in a Tysabri infusion log, and they must be  
13 willing to be periodically audited by Biogen Idec  
14 to ensure compliance with these requirements.

15 Another important component of these  
16 requirements is verifying the completion of a  
17 patient checklist before each dose in every  
18 patient, and I will describe this checklist on the  
19 next page.

20 [Slide.]

21 So, there are no proven monitoring  
22 methodologies for the early detection of PML. So,

1 in considering this challenge, we sought feedback  
2 from many neurologists.

3 Based on this, we determined that the best  
4 approach would be the monthly use of a  
5 questionnaire to screen patients for new or  
6 worsening neurological symptoms. If such symptoms  
7 are detected, we are instructing the Tysabri dosing  
8 be suspended immediately and that the patient be  
9 evaluated by their neurologist.

10 The questionnaire will be administered to  
11 each patient prior to each infusion. It may be  
12 administered either by the neurologist or his nurse  
13 in the office, or by phone, or by the infusion  
14 nurse in the infusion center setting.

15 We asked neurologists whether this  
16 questionnaire could always be done in person in the  
17 neurologist's office. Well, some neurologists liked  
18 this approach, others told us that in many practice  
19 settings, especially in rural areas, a requirement  
20 for a monthly visit to the neurologist would be a  
21 hardship for patients.

22 So, we felt that choices regarding the

1 mechanism for administering the questionnaire are  
2 important because not every patient has a neurology  
3 clinic nearby that they can visit on a monthly  
4 basis.

5           Therefore, the use of this questionnaire  
6 in the ways that I have described allows access to  
7 therapy to patients in a variety of locales and  
8 healthcare settings.

9           The patient checklist intent is to  
10 reinforce the importance of clinical vigilance and  
11 to facilitate a structured monthly interaction  
12 between the patient and the healthcare  
13 professional.

14           It is not meant to replace the  
15 neurologist's judgment, and so we are instructing  
16 the healthcare professional who administers this  
17 checklist to have a very low threshold, to contact  
18 the neurologist if there are any concerns that are  
19 detected on this checklist.

20           The additional purpose of the checklist is  
21 to reinforce the use of Tysabri as a monotherapy,  
22 and not in immunocompromised patients.

1 I will be happy to answer any questions  
2 about this checklist afterwards.

3 [Slide.]

4 So, now let me walk you through the  
5 controls that we have in our system.

6 Before a patient and physician begin  
7 Tysabri treatment, they will have a discussion  
8 about the risks and benefits of Tysabri. They will  
9 read and sign the patient-physician acknowledgment  
10 on the enrollment form, and they will send it to  
11 Biogen Idec.

12 Once we receive that form, we will verify  
13 that the patient-physician acknowledgment has been  
14 signed, and we will assign an authorization number  
15 to that patient. We will also match that patient  
16 to a registered infusion center and will notify  
17 that infusion center that this patient is eligible  
18 for Tysabri treatment.

19 How does an infusion center become  
20 registered? They have been trained by Biogen Idec  
21 on the appropriate use of Tysabri and the risks and  
22 benefits of Tysabri, and they have attested that

1 they will follow the requirements of the risk  
2 management plan.

3 They are now known to our controlled  
4 centralized distribution system, and we can begin  
5 shipping Tysabri to such a registered infusion  
6 center. Now the patient can begin Tysabri  
7 treatment.

8 So, clearly, as you can see, we have built  
9 several controls into the system. There is a  
10 control at the patient and at the physician level  
11 in terms of a mandatory enrollment into a registry.

12 There is a control at the infusion level  
13 because only registered infusion centers can  
14 administer Tysabri, and there is a control at the  
15 distribution level because we will deliver Tysabri  
16 only to registered infusion centers.

17 I should mention that we also evaluated  
18 proposals to ship Tysabri one vial at a time for  
19 each patient, and this is a relevant question,  
20 because it is a question that has been posed to the  
21 Advisory Committee.

22 We concluded that this would not enhance

1 the safety of the patients and would restrict  
2 access to Tysabri, because it would create a  
3 significant burden for infusion centers, especially  
4 those located in hospitals and in academic centers.

5 [Slide.]

6 Now, I will turn to our risk assessment  
7 plan.

8 [Slide.]

9 We have made a major commitment to further  
10 study the safety of Tysabri in the post-marketing  
11 setting. Our major studies are the Tysabri  
12 Registry and a Tysabri observational cohort study,  
13 which I will describe in the next few slides.

14 We also have additional studies planned  
15 that seek to understand the background rate of PML  
16 in MS patients, the impact of Tysabri on immune  
17 function, and the utility of various monitoring  
18 methodologies, such as plasma viral load testing  
19 and neurological questionnaires in clinical trials.

20 In the interest of time, I can't present  
21 these during my presentation, but I could answer  
22 any questions that you may have after the

1 presentation.

2 [Slide.]

3 So, the Tysabri Registry was designed to  
4 determine more precisely the incidence and risk  
5 factors for PML in Tysabri-treated patients and  
6 also the risk factors and incidence of other  
7 serious opportunistic infections.

8 Enrollment into this registry is mandatory  
9 for all physicians and all patients. We will be  
10 instructing physicians to report any PML event to  
11 Biogen Idec immediately, and in addition, we will  
12 be querying every patient, every physician on every  
13 patient every six months regarding the occurrence  
14 of any PML, any other serious opportunistic  
15 infection, any death of any cause, and any  
16 discontinuation of Tysabri treatment.

17 If a patient is discontinued, they must  
18 remain in the registry for a minimum of six months  
19 after the last dose, so we can collect the final  
20 set of data on this patient.

21 In addition, we will also collect all  
22 spontaneously reported events that occur in this

1 registry.

2 [Slide.]

3 We will follow up patient deaths through  
4 the National Death Index and collect death  
5 certificates on any patient that has died as an  
6 additional layer of diligence.

7 Noncompliance with the reporting of the  
8 data to us will result in de-enrollment of the  
9 physician and/or the patient.

10 So, this registry provides intense safety  
11 surveillance and tracking of all patients that  
12 exceeds routine pharmacovigilance activity.

13 [Slide.]

14 If a PML occurs in the registry, this is  
15 what we are going to do. We will thoroughly  
16 collect all data related to this case including  
17 results of clinical findings, source documentation  
18 of MRI findings, and results of CSF testing from JC  
19 viral DNA.

20 We will carefully analyze any PML case,  
21 looking for potential risk factors including  
22 underlying comorbidities or use of concurrent

1 therapies.

2 We will evaluate the case based on  
3 predefined criteria for PML that we have developed  
4 with PML experts, and if needed, we will seek  
5 external advice on any indeterminate cases.

6 We will report the case in an expedited  
7 fashion to the FDA, and because this registry will  
8 give us a complete denominator of all  
9 Tysabri-treated patients and complete ascertainment  
10 of every PML case, we will be able to assess the  
11 risk-benefit profile of Tysabri in an ongoing  
12 fashion, and if there is a clinically significant  
13 change to that risk-benefit profile, we can  
14 implement rapid corrective actions.

15 [Slide.]

16 Now, I will turn to the Tysabri  
17 Observational Cohort Study.

18 This study seeks to evaluate the long-term  
19 safety of Tysabri in the clinical practice setting.

20 A subset of patients in the Tysabri  
21 Registry will enroll into this voluntary  
22 observational cohort study.

1           We will enroll 5,000 MS patients  
2 worldwide, of which 3,000 will be enrolled in the  
3 U.S., and follow them for five years.

4           The size and scope of this study is such  
5 that it is powered to detect rare events occurring  
6 with an incidence of 0.06 percent.

7           In this study, we will collect all serious  
8 adverse events on all patients, as well as  
9 concomitant immunomodulatory and immunosuppressant  
10 therapies.

11           We will be able to assess the risk of  
12 serious infections and long latency events, such as  
13 malignancies.

14           Because we are collecting all serious  
15 adverse events, we will be able to investigate any  
16 potentially new safety signals that might arise in  
17 the post-marketing setting.

18           [Slide.]

19           Now, I will turn to the evaluation of our  
20 risk management plan.

21           [Slide.]

22           We have an evaluation plan that will

1 carefully monitor the success of our risk  
2 management efforts. It includes the analysis of  
3 data derived from the Tysabri Registry, as well as  
4 the results of surveys and audits.

5 We will share these data with the FDA  
6 every three months, and if needed, based on these  
7 data, we can implement rapid corrective actions to  
8 the plan, and this may include revised labeling  
9 and/or improvements in our risk minimization system  
10 or educational tools.

11 So, we will be continuously evaluating the  
12 success of our risk management efforts, and if we  
13 need to, make enhancements to the plan.

14 [Slide.]

15 So, in summary, our risk management plan  
16 seeks to inform and minimize the risk of PML. We  
17 are proposing mandatory registration of all  
18 prescribing physicians and all treated patients.

19 We are proposing monthly screening of  
20 patients in the infusion center setting through the  
21 use of a patient checklist. We have developed a  
22 controlled, centralized distribution system that

1 will allow us to know the location and number of  
2 all vials shipped, and we are mandating the use of  
3 Tysabri only in registered infusion centers that  
4 have attested that they will follow the risk  
5 management requirements.

6 We are also proposing an ongoing detailed  
7 assessment of the PML risk, as well as the overall  
8 safety of Tysabri.

9 We have an evaluation plan to monitor the  
10 success of our efforts, and we have designed this  
11 plan to ensure appropriate use of Tysabri without  
12 unnecessary burden to physicians or barriers to  
13 patient access.

14 [Slide.]

15 Now, in conclusion, based on the data that  
16 you have heard this morning, based on the unmet  
17 need in MS, based on the efficacy and safety of  
18 Tysabri, and the risk management plan that we have  
19 proposed, I will summarize our thoughts on the  
20 overall benefit-risk profile of Tysabri.

21 [Slide.]

22 There is no question that MS is a

1 devastating, progressively disabling neurologic  
2 disease with a very high unmet need.

3 Tysabri is a highly effective therapy with  
4 a benefit that is consistent in a broad range of  
5 subgroups.

6 PML is a rare but very serious risk of  
7 Tysabri treatment.

8 We are proposing a comprehensive risk  
9 management plan that seeks to minimize and to  
10 further assess this risk.

11 Based on this, we believe that Tysabri has  
12 a favorable benefit-risk profile that justifies its  
13 reintroduction into the U.S. market.

14 [Slide.]

15 Our recommendation is that Tysabri be used  
16 in the following way. It should be used in  
17 relapsing MS patients only as a monotherapy, not in  
18 patients who are known to be immunocompromised,  
19 only patients enrolled in the Tysabri Registry, and  
20 only in patients who are fully informed about the  
21 PML risk.

22 Based on Tysabri's benefit-risk profile

1 and the unmet need in MS, we believe that the use  
2 of Tysabri is justified in the following patients:

3           These are relapsing MS patients who either  
4 have disease activity on current therapy, or are  
5 intolerant of current therapy, or have high disease  
6 activity and our naive patients.

7           Now, we believe that most of Tysabri's use  
8 will occur in these three categories of patients,  
9 however, we also recognize that starting a  
10 disease-modifying therapy for MS is a complex  
11 decision, and so we think that Tysabri should also  
12 be available to other relapsing MS patients that  
13 may be deemed appropriate based on individual  
14 benefit-risk assessments made by their physician  
15 and by the patient.

16           Therefore, we are seeking indication for  
17 use of Tysabri in patients with relapsing MS.

18           On behalf of Biogen Idec and Elan, I would  
19 like to share with you that the needs of MS  
20 patients and physicians have weighed heavily on us  
21 as we contemplated the best path forward for  
22 Tysabri, and we look forward to hearing the

1 Advisory Committee's views on this important  
2 subject.

3 [Slide.]

4 I have the pleasure of introducing Dr.  
5 Rudick, who is a neurologist at the Cleveland  
6 Clinic, specializing in the treatment of multiple  
7 sclerosis. Dr. Rudick directs the Mellen Center,  
8 where he conducts his research and sees patients  
9 with MS referred from around the world.

10 He is also Director of the Division of  
11 Clinical Research at his institution, and in that  
12 capacity, he oversees clinical research programs at  
13 the Cleveland Clinic, which includes over 1,000  
14 clinical trials involving over 20,000 research  
15 subjects.

16 For over 20 years, Dr. Rudick's research  
17 has focused on clinical trials, clinical and  
18 imaging outcome measures, and biologic markers of  
19 the MS disease process.

20 He participated in the design of the 1801  
21 and 1802 studies. He was the coordinating  
22 investigator and chair of the Advisory Committee

1 for the 1802 study, and is the lead author on the  
2 recently published report of the 1802 study in The  
3 New England Journal of Medicine.

4 We are pleased to have Dr. Rudick with us  
5 today.

6 Clinical Perspective

7 DR. RUDICK: Good morning. Thank you for  
8 listening to my professional opinion about Tysabri  
9 and multiple sclerosis.

10 I am going to make three points and I will  
11 speak briefly.

12 First, I would like to point out from my  
13 perspective the magnitude of the unmet need in the  
14 MS field.

15 Secondly, I will explain why Tysabri is an  
16 important new therapeutic option in MS.

17 Finally, I will give my views on what  
18 constitutes responsible use of Tysabri.

19 I will speak about each of these in turn,  
20 again, quite briefly.

21 My point about the unmet need is really  
22 very simple. Despite the approved

1 disease-modifying drugs that we have available, MS  
2 remains in far too many patients a horrible  
3 disease, and there is a very huge unmet need.

4           The available drugs are effective and we  
5 are all very grateful to have these drugs, we  
6 didn't have them 10 years ago, but they are far  
7 from adequate.

8           The Phase III placebo-controlled clinical  
9 trials have demonstrated that the current drugs are  
10 one-third effective in reducing the relapse rate.

11           The effect of these drugs is so modest  
12 that we endlessly debate at our MS meetings the  
13 long-term relevance of the benefits of the current  
14 drugs, but we have used these drugs long enough to  
15 know they don't stop the progression of the  
16 disease, and we have no debates about that at our  
17 MS meetings.

18           In my experience during 10 years of using  
19 the MS drugs, I have noticed that most patients  
20 have relapses or eventually progression of their  
21 disability despite their adherence to the  
22 prescribed drugs.

1 Patients who seem stable clinically often  
2 show silent MRI lesions and too often later enter a  
3 stage of progressive disability, so the appearance  
4 of stability early on with these drugs sometimes is  
5 illusory.

6 These experiences are really not  
7 surprising. One only has to look at the Phase III  
8 clinical trial data. In addition to that, the  
9 current drugs cause side effects that diminish  
10 quality of life, and many patients simply  
11 discontinue their use.

12 My clinic is filled with patients, MS  
13 patients who report disease activity despite the  
14 current drugs, patients similar to the ones who  
15 entered the 1802 clinical trial. In such patients,  
16 our options include switching between the drugs or  
17 using our drugs in combinations.

18 Switching is of little benefit in my  
19 opinion given the modest differences, if any,  
20 between our available drugs. Combining interferon  
21 or glatiramer acetate with steroids, azathioprine,  
22 or methotrexate might help, but there is no data to

1 support this approach, and there are questions  
2 about safety.

3 Mitoxantrone is approved for relapsing  
4 progressive MS, but has significant cardiac  
5 toxicity, and there are cases of acute leukemia  
6 that have been reported.

7 The bottom line is that approved therapies  
8 don't come close to addressing our unmet need in  
9 multiple sclerosis. Many, maybe most, MS patients  
10 need better options, and we need new therapeutic  
11 products.

12 Now, let me explain why I think Tysabri is  
13 an important new therapeutic option for patients  
14 with MS.

15 The 1801 study, natalizumab versus  
16 placebo, was the first Phase III  
17 placebo-controlled, randomized clinical trial in MS  
18 in almost a decade.

19 The robust clinical trial results met with  
20 widespread excitement and enthusiasm by doctors and  
21 patients who viewed Tysabri as a major therapeutic  
22 advance, and you have heard that 7,000 patients

1 signed up for Tysabri within just a few months.

2 I believe there were three reasons for

3 this widespread view which I happen to share.

4 First, the beneficial effect on relapses, over a  
5 two-third reduction, was double what we have seen  
6 in all of the studies of the approved drugs.

7 Three independent randomized,  
8 placebo-controlled Phase III studies of interferon  
9 and a Phase III glatiramer acetate study, each  
10 separately and individually showed about a  
11 one-third reduction in relapses.

12 The difference observed in the Tysabri  
13 monotherapy study was over a two-third reduction.  
14 I am very well aware of the hazards and  
15 uncertainties of comparing results across studies,  
16 but in comparison with every other large Phase III  
17 placebo-controlled trial, the two-third reduction  
18 in relapse rate simply cannot be ignored. It is a  
19 striking result from my perspective.

20 Second, the 1802 add-on study enrolled  
21 patients who had experienced disease activity while  
22 using, and presumably gaining some benefit, from

1 standard therapy.

2 Addition of Tysabri to standard therapy in  
3 these patients substantially reduced clinical and  
4 MRI disease activity compared with the standard  
5 therapy alone. This indicates that Tysabri  
6 provided substantial incremental benefit over  
7 standard therapy alone.

8 Third, many patients simply don't perceive  
9 benefits from current MS drugs or don't tolerate  
10 them and have stopped therapy entirely. These  
11 patients need options that they will accept and  
12 that they can tolerate.

13 Now, in this regard, in the Tysabri  
14 clinical trials, we observed significant benefits  
15 and validated patients self-reported quality of  
16 life scales, including our pain and fatigue scales.  
17 We have never previously observed such benefits in  
18 MS studies in the past, and I found this extremely  
19 encouraging.

20 Tysabri really looks like a major  
21 therapeutic advance and the question then on  
22 everyone's mind is does the benefit and the promise

1 that Tysabri will actually help people justify the  
2 risk of PML, which is currently estimated at 1 in  
3 1,000.

4 To answer this question, which is not an  
5 easy question, I believe it's important to balance  
6 benefits with the risk.

7 I estimated crudely the benefit that might  
8 result in 1,000 patients treated for two years  
9 compared with standard therapy. Based on the  
10 clinical trials, about 400 relapses would be  
11 prevented in 1,000 patients if they used Tysabri as  
12 opposed to standard therapy. How many of these  
13 patients would remain functional, how many would  
14 remain independent, how many would remain employed,  
15 and what would the long-term benefit be?

16 These estimates would really be quite  
17 speculative, but the gains could very well be  
18 substantial, and I believe gains, such as this,  
19 have to be factored in to the overall assessment.

20 So, I have mentioned the magnitude of the  
21 unmet need and explained why I think that Tysabri  
22 is an important new option. Let me explain what I

1 think about the responsible use of Tysabri.

2 First, I don't believe that Tysabri use  
3 should be tied to a requirement that the risk of  
4 PML be eliminated. From the data that I have seen,  
5 I don't believe this is a realistic requirement,  
6 but I do believe Tysabri should be used in  
7 appropriate patients who are fully informed and  
8 carefully monitored by an accessible neurologist.

9 I have subscribed during my career to a  
10 basic tenet of the therapeutic relationship with my  
11 patients. I communicate with them, and we make  
12 joint decisions about disease management. We do  
13 that together.

14 So, I asked my patients whether they would  
15 want to take a new drug that might be twice as  
16 effective as their standard therapy, but carries a  
17 risk of 1 in 1,000 of a fatal brain infection.

18 My patients had very little difficulty,  
19 surprisingly, answering that question. They gave  
20 prompt and fairly definitive answers. Some said  
21 they would welcome the chance to use a more  
22 effective therapy even under those conditions, and

1 others said no, they wouldn't take it.

2           Every patient that I talked with seemed to  
3 grasp the situation pretty easily. They weighed  
4 the options and they decided whether the benefit to  
5 them was worth the risk to them in the context of  
6 their disease state, their personal situation,  
7 their value system, their family, and whatever  
8 other factors were important to them.

9           I believe the neurologist has to decide  
10 whether Tysabri is an appropriate option, but I  
11 think the patient needs to be a full participant in  
12 deciding in that situation whether to use the drug.

13           Now, if the use of Tysabri is appropriate  
14 in a given patient, and the patient understands and  
15 accepts the risk, and agrees to monitoring, I  
16 believe treatment should proceed.

17           Let me sum up by just saying that Tysabri  
18 offers the likelihood of significant benefits  
19 because it is a therapeutic advance in a disease  
20 with a major unmet need. I believe it should be  
21 available to for responsible use under the  
22 conditions I outlined, because MS in many patients

1 is not adequately controlled on established  
2 therapies.

3 There really is no good evidence-based  
4 options for many of these patients, and  
5 neurologists can and will, I believe, use Tysabri  
6 responsibly.

7 I would just close by urging the panel to  
8 recommend the release of Tysabri for clinical use,  
9 along with some guidelines to promote its safe use,  
10 and I appreciate your listening to my opinion.

11 Thank you.

12 DR. KIEBURTZ: Thank you, Dr. Rudick.

13 We will now have a question period from  
14 the Committee. Just a couple of things. We will  
15 stop in 15 minutes. Just to remind members and  
16 consultants, I will read a little thing here that  
17 this is about a transparent process for information  
18 gathering and decision-making, which means outside  
19 of the context of the public hearing, we shouldn't  
20 speak with one another about our thoughts, or with  
21 people outside the committee.

22 The intent of the committee is that those

1 deliberations happen in the public eye. I mean we  
2 can certainly talk with one another, and other  
3 friends and colleagues, but the substance of the  
4 meeting is to not be conducted outside of the  
5 public hearing.

6 So, when we break after the questions,  
7 that is the time to stop deliberating, and then  
8 pick it up again when we join, and similarly, this  
9 evening, right through to the end of the meeting.  
10 So, just as a reminder about that.

11 Secondly, do remember that we won't be  
12 able to answer everyone's questions in the context  
13 of these 15 minutes. I am sure the sponsor and  
14 their representatives and the FDA will be here  
15 throughout the day tomorrow. When we have  
16 questions, they will be ready to answer them at  
17 that time, so don't think this is our last  
18 opportunity to ask questions.

19 Questions from Committee to Sponsor

20 DR. KIEBURTZ: Dr. Sacco, I cut you off.  
21 You had a question when we last opened.

22 DR. SACCO: I had a question for the

1 safety. One of the slides, I think it was Slide  
2 50, demonstrated a cumulative risk of any  
3 infections, and I assume that was like any  
4 infection, but no cumulative risk of some composite  
5 of serious infections including the opportunistic  
6 ones.

7 Do you have any slide, such as that, where  
8 you would combine together some of the  
9 opportunistic infections including some of the ones  
10 you have mentioned on herpes, PML, and others?

11 DR. PANZARA: Yes, we do. That would be  
12 Slide 14-33, please.

13 [Slide.]

14 This slide is similar to the common  
15 infections. This is all serious infections reported  
16 in the placebo-controlled trials of multiple  
17 sclerosis. Again, the Kaplan-Meier curves  
18 represent the cumulative probability of a serious  
19 infection over the 120-week dosing interval.

20 As one can see, the curves are quite  
21 similar, and similar to the common infections, the  
22 hazard ratio was approximately 1, indicating an

1 equal risk.

2 DR. KIEBURTZ: Dr. Hughes.

3 DR. M. HUGHES: I had a question about the  
4 rates of PML and other information that you might  
5 have.

6 Obviously, the rate that is being  
7 suggested of 1 in 1,000 person years of follow-up  
8 is assuming that the risk is independent of the  
9 duration of drug exposure, and it is notable that  
10 the two events of PML in MS patients occurred two  
11 or three years out.

12 So, playing the devil's advocate, the risk  
13 could be actually substantially higher than the 1  
14 in 1,000 if the risk accumulates over time. I  
15 wondered what information you had about changes in  
16 PK or changes in immunologic status out through two  
17 or three years.

18 DR. PANZARA: Well, we calculated the rate  
19 in a variety of ways, and we felt that given that  
20 one of the cases that developed PML had 8  
21 infusions, and the others had 20 to 30, that all  
22 should be incorporated, but we also calculated the

1 rate in terms of patients who receive combination,  
2 patients who had over two years of exposure.

3 The rate in all patients was about 0.5 per  
4 1,000 patient years for PML in the whole  
5 population. It's about 0.6 if you look at the  
6 patients who have had over two years, 0.65 to be  
7 exact, so we have done that analysis.

8 In terms of immunological changes over two  
9 years, we haven't done longer term immunological  
10 studies at that time point, but part of what we are  
11 planning to do in the post-marketing setting is to  
12 do additional immunological testing, as Dr. Bozic  
13 indicated.

14 Finally, in terms of the PK, we determined  
15 that the concentration of drug in the serum of the  
16 patients who developed PML were right at the median  
17 for the overall population, so there did not appear  
18 to be an increase in drug concentration.

19 DR. M. HUGHES: Is the median changing  
20 over time within the population?

21 DR. PANZARA: No, the median remains  
22 relatively constant throughout. There is some

1 accumulation, but that levels off at about nine  
2 months and remains constant.

3 DR. KIEBURTZ: Dr. McArthur.

4 DR. McARTHUR: What would be your  
5 recommendations for intravenous methylprednisolone  
6 for concurrent use of steroids?

7 DR. SANDROCK: So, I.V. methylprednisolone  
8 at a gram per day for three to five days was  
9 allowed in the protocol for the treatment of  
10 relapses, and we saw an increase in infections in  
11 patients who were on steroids during the time that  
12 they were treated, but the increase was similar in  
13 both the placebo group and the natalizumab, so we  
14 believe that the use of steroids for the treatment  
15 of relapses is appropriate, intermittent steroids.

16 DR. McARTHUR: So, in the risk management  
17 plan, will there be any monitoring of the use of  
18 steroids, any recommendations for the maximum  
19 number of annual courses of steroids?

20 DR. SANDROCK: Dr. Bozic.

21 DR. BOZIC: We are warning against the use  
22 of Tysabri with concurrent immunosuppressants, and

1 we would classify chronic oral steroids in that  
2 category, so we don't want people to use Tysabri in  
3 combination with chronic steroids or monthly pulse  
4 steroids. That would not be allowed.

5 DR. KIEBURTZ: Just a quick comment to the  
6 committee members. If you want to speak, just put  
7 your hand up. Sohail and I will make eye contact  
8 with you, and we have got you on the list, and I  
9 will run down the list.

10 So, Dr. Goldstein.

11 DR. GOLDSTEIN: I probably have 15 or 20  
12 minutes worth of questions myself, but obviously, I  
13 won't do that.

14 One thing I would like to sort of flesh  
15 out a little bit. We talked a lot about risk and  
16 benefit, and it's risk for what and benefit for  
17 what is the basic issue.

18 Now, we know that there are other  
19 disease-modifying therapies, as Dr. Rudick had  
20 carefully pointed out, so if you could translate  
21 these data from hazard ratios into numbers needed  
22 to treat as best you can, and I realize, you know,

1 again, that there is a big difficulty here.

2 We are taking trials that were done a  
3 decade apart in different patient populations and  
4 trying to extrapolate this, but how many people  
5 would you need to treat to prevent one relapse over  
6 two years with this drug as opposed to the  
7 available other drugs?

8 How many people would you need to treat  
9 over two years to prevent one patient from going on  
10 to a clinical relapse? How many people would you  
11 need to treat over two years to prevent one patient  
12 from reaching disability, because I think that's  
13 the numbers that patients and we need to know as we  
14 are trying to balance these risk and benefits?

15 DR. SANDROCK: If I could show Slide  
16 16-65.

17 [Slide.]

18 This kind of gets at what you would like,  
19 I think. For every 1,000 patients treated with  
20 natalizumab for two years compared to no treatment,  
21 we estimate there will be 1,000 fewer relapses, 260  
22 more patients remaining free of relapse, 120 more

1 patients remaining free of progression by 1 point  
2 on the EDSS scale, 60 fewer hospitalizations due to  
3 MS relapse, and 40 fewer patients requiring aids  
4 for ambulation.

5 That is compared to a 0.1 percent  
6 approximate risk of PML, and a 4 percent risk of  
7 hypersensitivity reaction.

8 DR. GOLDSTEIN: That is sort of getting  
9 what I was getting at, but not quite.

10 DR. SANDROCK: Okay.

11 DR. GOLDSTEIN: What I want to know is not  
12 compared to placebo, because the study,  
13 unfortunately, was done compared to placebo, but we  
14 are not offering it compared to placebo, we are  
15 offering it compared to other established  
16 therapies.

17 So, if you redid those numbers again and  
18 change it around a little bit, how many people  
19 would you need to treat to prevent 1 person from  
20 going on to each one of those endpoints. You may  
21 not have the numbers now, but if you could come  
22 back with them later, that's fine.

1 DR. SANDROCK: Actually, I do have a slide  
2 with the number in it to treat.

3 Okay. We will have to get back to you.

4 DR. KIEBURTZ: Dr. Porter.

5 DR. PORTER: For Dr. Bozic, a very  
6 practical question. You talked briefly about the  
7 patient who comes back to the clinic, who is  
8 slightly ill, and then the patient was, in your  
9 scenario, kind of assumed to possibly have PML.

10 Now, there is obviously perhaps only a  
11 narrow overlap between the signs and symptoms of  
12 PML and MS, but let's assume that this patient  
13 comes in with an increase in confusion, just to  
14 make the issue more difficult.

15 How are you going to instruct your  
16 neurologist to deal with this issue when the  
17 overlap is difficult between the relapse, which you  
18 like to treat, and the PML, which is very unlikely,  
19 but you would prefer not to treat with Tysabri?

20 DR. BOZIC: We will have an extensive  
21 continued medical education program directed at  
22 physicians, and a core feature of that program will

1 be a PML diagnostic algorithm that will outline the  
2 scenarios for the workup of a patient who  
3 potentially might have PML.

4 The confirmation of a PML diagnosis must  
5 rely on a triad of clinical findings, MRI findings,  
6 and then documentation of JC viral DNA in the  
7 central nervous system.

8 I think Dr. Panzara can speak a bit more  
9 about the diagnostic algorithm.

10 DR. PANZARA: As Dr. Bozic indicated, I  
11 think we learned a great deal about making the  
12 diagnosis. I think what we are trying to do at  
13 this stage is to have a sufficiently low threshold,  
14 such that we are not trying to have the  
15 determination of PML or MS immediately at the time  
16 of infusion. We are trying to find a change that  
17 would prompt the workup using the tools to make the  
18 diagnosis.

19 So, that has been our approach. We want  
20 to have a sufficiently low threshold to prompt  
21 physician assessments and then the additional  
22 components of the triad, such as MRI and spinal

1 fluid.

2 DR. PORTER: This means that you might  
3 treat a patient who actually has PML, and then make  
4 the diagnosis later.

5 DR. PANZARA: No, actually, we are asking  
6 any change at all, not making a determination of  
7 whether it's MS or PML, any suspicious change or  
8 any change at all, for that matter, that would  
9 prompt a physician assessment and an evaluation,  
10 and if there is uncertainty about change or if  
11 there is a neurological change, a physician should  
12 have a very low threshold to do an MRI, and suspend  
13 dosing is the first thing that must be done.

14 DR. SANDROCK: Could I add to that?

15 DR. KIEBURTZ: Yes.

16 DR. SANDROCK: Our clinical trial data  
17 indicate that the annualized relapse rate on  
18 natalizumab treatment is 0.2, which translates to 1  
19 relapse every five years.

20 So, it will happen, but as Dr. Panzara and  
21 Bozic said, any new change should prompt an  
22 evaluation with suspension of dosing.

1 MS. SITCOV: I have just a two-part  
2 question.

3 Is there a recommendation for assuming, if  
4 this were approved, for how long someone should be  
5 off one of the current MS disease, modifying  
6 diseases? That is number 1.

7 Number 2, of the 7,000 MS patients who  
8 took Tysabri, I guess some may have only gotten 1  
9 dose, were they given the Tysabri by a neurologist,  
10 number 1, and is it possible that of those 7,000,  
11 there was another case of PML that was not  
12 reported?

13 DR. SANDROCK: In terms of the washout  
14 period from a current therapy to Tysabri, we are  
15 suggesting a two-week washout period based on the  
16 PK and the pharmacodynamic effects of these drugs,  
17 a two-week washout period.

18 I think the second part of your question  
19 referred to the 7,000 patients and whether or not  
20 there were any cases of PML.

21 MS. SITCOV: Unreported.

22 DR. SANDROCK: Unreported. Any suspicious

1 case was brought forward to the IAC, and we  
2 evaluated a few post-marketing cases at the IAC  
3 level, and they were excluded.

4 MS. SITCOV: Right, but were those, the  
5 7,000 that were prescribed, in all those cases,  
6 would they have been prescribed by a neurologist or  
7 sometimes by a general practitioner?

8 DR. SANDROCK: We believe that the vast  
9 majority--

10 MS. SITCOV: Who would not be as familiar.

11 DR. SANDROCK: The vast majority of  
12 patients were prescribed by neurologists.

13 DR. PANZARA: I would just like to add to  
14 that, if I could, that upon the dose suspension,  
15 anyone who prescribed natalizumab was sent a  
16 Healthcare Provider letter immediately, outlining  
17 the steps to be taken should they be suspicious for  
18 PML, and that includes referral to the IAC, as well  
19 as the clinical MRI, spinal fluid steps to be  
20 taken, so we are quite confident that if there are  
21 other cases out there, they would have been  
22 referred.

1 MS. SITCOV: So, that was all voluntary.

2 DR. PANZARA: It was a voluntary request,  
3 yes.

4 DR. KOSKI: I would like to actually  
5 expand on the question that was just asked. In  
6 terms of the prior therapy and selection of the  
7 patients to go on Tysabri, obviously, I think you  
8 are talking about one of the ABC drugs, but I would  
9 like to also address the issue about other  
10 cytotoxic drugs.

11 Obviously, the patient with Crohn's  
12 disease had been off those drugs for eight months  
13 before, and actually, although it was said that the  
14 patient had lymphopenia at the time that the  
15 patient came in with JC virus manifestations and  
16 PML, did not have lymphocytopenia, so would you  
17 handle patients on those two different types of  
18 drugs differently?

19 DR. SANDROCK: Yes, if a patient had been  
20 on the cytotoxic drugs, such as cyclophosphamide,  
21 the washout period would need to be longer, at  
22 least a month, and we would also recommend taking a

1 white count prior to starting Tysabri.

2 So, I think the washout period is going to  
3 depend a lot on the drug that they are washing out  
4 from.

5 DR. KOSKI: But I would say that in that  
6 particular patient, neither of those measures would  
7 have been adequate.

8 DR. SANDROCK: Well, actually, a white  
9 count and looking at the lymphocyte fraction,  
10 probably would have excluded that patient.

11 DR. KIEBURTZ: Dr. Couch.

12 DR. COUCH: MS is a long-term disease with  
13 significant survival rate over 20 and even 30  
14 years. Do you feel that you have a decent handle  
15 on the possible genesis of malignancy by Tysabri  
16 therapy, or can you give us any additional insight  
17 on the potential for creating malignancy that is  
18 inherent in this entire group of anti-immune drugs?  
19 Can you give us any other insight about this?

20 DR. SANDROCK: Well, the only data we have  
21 are from our clinical trials right now, and we see  
22 a balanced incidence of the malignancy. It's a

1 drug that affects the immune system, cell-mediated  
2 immunity. It's possible that in the future, we  
3 will see something, but so far we have not seen a  
4 signal in terms of malignancy.

5 DR. KIEBURTZ: Last question is Dr.  
6 McArthur.

7 DR. SANDROCK: By the way, I would like to  
8 add that the observational cohort study will  
9 provide a lot more information on rare events like  
10 this over the long term.

11 DR. MCARTHUR: This is a question for Dr.  
12 Bozic about the risk management plan, and apart  
13 from optic neuritis, I can't think of any symptom  
14 that would distinguish PML from multiple sclerosis.

15 So, one of my questions relates to the  
16 emphasis on the vigilance and the administration of  
17 the questionnaire prior to Tysabri, and for  
18 patients who have emotionally, psychologically  
19 bought into Tysabri, there is a strong emphasis on  
20 not reporting symptoms, because patients will know  
21 that if they report them, it might trigger  
22 discontinuation of Tysabri.

1           So, in your focus groups and your  
2   consideration, how have you incorporated that into  
3   your plan?

4           DR. BOZIC: In talking to many patients,  
5   it is very clear that they are very concerned about  
6   the risk of PML, and a primary goal of our risk  
7   management efforts is to fully inform patients  
8   about the risk of PML, not only prior to the start  
9   of therapy, but to reinforce that information at  
10  every dose.

11           So, the infusion centers must send out a  
12  Medication Guide that describes the risk of PML at  
13  every dose, and the patient checklist also  
14  documents that the patient has read that Medication  
15  Guide before every dose, so we are continuously  
16  reinforcing the PML risk.

17           So, we think it's unlikely that a patient  
18  will answer, you know, try and game the checklist,  
19  if you will.

20           DR. KIEBURTZ: I want to thank the sponsor  
21  for their timely and lucid presentations and  
22  answering our questions. We are going to stop

1 questions for now. I presume you will be available  
2 as we deliberate tomorrow to answer further  
3 questions as they arise.

4 We will break for 15 minutes and we will  
5 start promptly in 15 minutes from right now.

6 [Break.]

7 DR. KIEBURTZ: Our first speaker from the  
8 FDA will be Dr. Susan McDermott giving the  
9 background as a clinical reviewer.

10 FDA Presentation

11 Background, Efficacy, and PML

12 DR. McDERMOTT: Good morning. Welcome to  
13 Maryland. My name is Susan McDermott. I am a  
14 neurologist and a clinical reviewer in the Division  
15 of Neurology Products.

16 [Slide.]

17 Today, I am going to talk to you about  
18 efficacy and PML that is associated with  
19 natalizumab.

20 [Slide.]

21 This is an outline of my talk, and the  
22 sponsor has provided much of the background

1 information regarding efficacy and safety, so we  
2 thought it would be most helpful to the committee  
3 if we just gave you our view of the data and filled  
4 in some information where appropriate.

5 So, first, I am going to just speak  
6 briefly about the regulatory background and then I  
7 am going to touch on the pivotal trials, the  
8 efficacy results, and then mention a word or two  
9 about the antibodies.

10 Then, we will discuss the PML cases, and  
11 we will also talk about the safety evaluations that  
12 the sponsor has performed.

13 [Slide.]

14 So, first, the regulatory background. The  
15 first question we are asking the committee is: Has  
16 the company fulfilled their commitment to show a  
17 sustained clinical benefit for two years, or at two  
18 years?

19 So, I thought that it may be helpful to  
20 you to talk just a little bit about the accelerated  
21 approval and what that commitment was.

22 As you know, accelerated approval is

1 allowed under the FDA regulations, and there were  
2 many factors that went into the approval, the main  
3 one being that natalizumab effect at one year was  
4 reasonably likely to predict the effect at two  
5 years.

6 I also wanted to just point out that the  
7 primary endpoints for MS therapy trials, what we  
8 consider at the FDA what is appropriate from a  
9 regulatory standpoint has to do with relapse rate  
10 and disability accumulation. Essentially, we  
11 require sponsors to show an effect on relapse rate  
12 or disability accumulation.

13 [Slide.]

14 So, we will move now to the efficacy. As  
15 you know, you have heard this presentation before,  
16 so I am just going to go through this quickly.

17 Study 1801 was one of the big pivotal  
18 trials. That was a monotherapy trial of natalizumab  
19 versus placebo, and as you can see, the patients  
20 were randomized in a 2:1 fashion, natalizumab to  
21 placebo.

22 What I have on this slide is the sustained

1 disability progression, which was the primary  
2 outcome at two years, and I also have the primary  
3 outcome for the first year analysis. That was the  
4 annualized relapse rate.

5           What I should tell you upfront is that our  
6 statistician, Dr. Sharon Yan, in particular, has  
7 taken the raw data from the sponsor and has  
8 analyzed, on her own, according to the protocol, to  
9 look at the primary outcome and the top ranked  
10 secondary outcome, annualized relapse rate, and her  
11 analysis is consistent with the sponsor's analysis.

12           So, after they have given that exhaustive  
13 detailed presentation, I can easily now say we  
14 generally agree, so it makes my presentation much  
15 easier.

16           So, what I have on this slide is the  
17 absolute difference in sustained disability  
18 progression, and you will recall on their slide,  
19 they presented Kaplan-Meier curves showing a 42  
20 percent reduction in risk of reaching sustained  
21 disability at two years, and our analysis agrees  
22 with that.

1           Also, annualized relapse rate, which was  
2     the primary outcome at one year, and the top ranked  
3     secondary outcome at two years, they found a  
4     relative 68 percent reduction in relapse rate. We  
5     also found the same reduction.

6           [Slide.]

7           So, likewise, 1802, that's the combination  
8     trial. You will remember all patients in this study  
9     were on Avonex and had been on Avonex for at least  
10    a year, however, they were continuing to have  
11    breakthrough relapses on Avonex, and so these  
12    patients were randomized 1:1 to receive natalizumab  
13    plus Avonex, or placebo plus Avonex.

14          So, again, I have the primary outcome at  
15    two years, as well as the primary outcome at one  
16    year, which is also the top ranked secondary  
17    outcome at two years, the annualized relapse rate.

18          Again, our analysis agrees with the  
19    sponsor's analysis. You may recall what they  
20    found, in Study 1802, is a 24 percent reduction in  
21    the risk of disability progression at the end of  
22    two years, and in the relapse rate, they also found

1 a 55 percent relative reduction in relapse rate,  
2 and our analysis agrees with that. So, that was  
3 relatively easy.

4 [Slide.]

5 Now, I am going to switch and just mention  
6 a word about anti-natalizumab antibodies, and the  
7 speaker to follow, Dr. Hughes, is going to speak  
8 more about the antibodies.

9 But I wanted to say that in the pivotal  
10 trials, the sponsor looked for evidence of  
11 anti-natalizumab antibodies, and they found that 6  
12 percent of patients developed persistent  
13 antibodies, and what I mean by that, "persistently  
14 positive antibodies," is that they tested positive  
15 on at least two occasions.

16 So, an interesting finding, when they did  
17 a subgroup analysis, is that patients who tested  
18 persistently positive for these antibodies, there  
19 was an association with less efficacy compared to  
20 antibody-negative subjects.

21 [Slide.]

22 I am going to try to summarize now

1 efficacy, and I will start with relapse rate. That  
2 was the primary outcome at one year, and it was the  
3 top ranked secondary outcome at two years, and you  
4 will recall in Study 1801, that's the big  
5 monotherapy study of natalizumab versus placebo,  
6 there was a 68 percent relative decrease in  
7 annualized relapse rate at two years.

8           In Study 1802, there was a 55 percent  
9 relative decrease in annualized relapse rate at two  
10 years. The relapse rate also slightly decreased  
11 during the second year.

12           One thing that our statisticians have done  
13 is we looked at the relapse rate during the first  
14 year, and compared it to the relapse rate during  
15 the second year, meaning from day zero to the end  
16 of Year 1 compared to the beginning of Year 2 to  
17 the end of Year 2.

18           What we found is that the relapse rate  
19 during the second year actually goes down a little  
20 bit, but just by a few percentage points, but it  
21 remains statistically compelling.

22           Also, I would say that the relapse rates

1 that you have heard, these relative decreases, 68  
2 percent and 55 percent, have been estimated  
3 approximately twice the treatment effect of other  
4 approved therapies that are available now.  
5 However, there are no head-to-head trials of  
6 natalizumab versus those approved therapies.

7 So, the next, my disability progression, I  
8 would like to have you recall that in Study 1801,  
9 there was a 42 percent reduction in the risk of  
10 sustained disability over two years, and in 1802,  
11 the combination trial, we found a 24 percent  
12 reduction in sustained disability progression over  
13 two years.

14 The treatment effect in 1801 was larger,  
15 but again, if you will recall, the populations were  
16 slightly different. The patients in 1802 had been  
17 on Avonex for at least a year and had continued to  
18 have breakthrough disease.

19 Now, add-on therapy. One of the most  
20 exciting potentials for natalizumab was the idea  
21 that it could fulfill an unmet need for combination  
22 therapy. As you know, I think most of the

1 committee members know that the currently approved  
2 MS drugs have not been shown to be effective using  
3 combination.

4           So, we were initially excited to think  
5 that natalizumab may show a benefit as a  
6 combination drug. So, when you look at 1802, it  
7 does win on the primary outcome, however, in one  
8 sense, we have limited data, so if you will  
9 remember the design of the study, all the patients  
10 were on Avonex, and then they were randomized to  
11 receive either natalizumab or placebo.

12           So, what we can say from that is we think  
13 we know a little bit about what happens when you  
14 add natalizumab to a patient who is on Avonex, but  
15 we don't know the opposite of what happens to  
16 patients who are on natalizumab and you add other  
17 therapies.

18           Also, if you will recall, the study was  
19 not really a factorial design. There was no  
20 natalizumab-only arm, there was no placebo arm, so  
21 it's difficult to draw a lot of conclusions about  
22 add-on therapy. One thing we can say is that we

1 are not really certain that the benefit of  
2 combination therapy is greater than the benefit  
3 that you gain from monotherapy.

4 Finally, with immunogenicity, what I would  
5 like to say is that there have been a small number  
6 of patients in the pivotal trial, 6 percent, who  
7 tested positive for anti-natalizumab antibodies,  
8 and a subgroup analysis showed a lower efficacy in  
9 these patients compared to those on placebo.

10 [Slide.]

11 So, now we are going to move on to PML.  
12 In addition to the committee members, I know there  
13 are a lot of people in the audience today, patients  
14 with MS, some of whom have been on natalizumab, and  
15 perhaps family members and friends of the three  
16 patients that I am going to discuss.

17 I understand that this can be a very  
18 difficult two days for you, particularly the  
19 discussion of PML, and in medicine, when we  
20 describe such tragedies, it can often appear very  
21 cold and clinical, so I certainly don't intend it  
22 to appear this way, and I apologize in advance

1 about the sterile nature of my presentation, but  
2 let's begin.

3 All committee members have received copies  
4 of the case reports, so I am just going to  
5 summarize these briefly and point out some of our  
6 thinking on these cases.

7 The first case was a 46-year-old lady with  
8 relapsing-remitting MS who was in Study 1802, and  
9 as you will recall, 1802 is the combination therapy  
10 trial. So, she was on Avonex, and she also  
11 received natalizumab.

12 She received a total of 37 infusions from  
13 April 2002 through January 2005.

14 In November of 2004, her PML symptoms  
15 began, and initially, they were thought to be  
16 worsening MS. This is one thing that I would like  
17 to point out to you that caught our eye initially  
18 as we began to go through the cases, keep in the  
19 back of your mind, is how are neurologists, how are  
20 physicians going to be able to discriminate MS  
21 versus early PML.

22 So, I will move on. The patient continued

1 to worsen. In December 2004, she had MRI changes  
2 that were atypical for MS. She received two short  
3 courses of steroids in December and January, and  
4 then in February, the patient passed away.

5 She did have positive JC virus in her CSF,  
6 and as you will recall from the sponsor's  
7 presentation, when the retrospective analysis was  
8 done on her blood, the serum was not positive for  
9 JC virus prior to diagnosis.

10 [Slide.]

11 The second case is a 46-year-old gentleman  
12 with relapsing-remitting MS, who was also in Study  
13 1802, and he received a total of 28 doses of  
14 natalizumab from October 2002 to December 2004.

15 In October 2004, he was found to have an  
16 atypical frontal lesion on routine MRI. This is  
17 another thing I would like for you to keep in the  
18 back of your mind that caught our eye as we were  
19 going through these cases.

20 This is a patient who was asymptomatic and  
21 had a funny lesion on his--or I should say an  
22 atypical lesion on his routine MRI scan. At that

1 time, PML was not thought of as a possibility.

2 Then, in November of 2004, subtle

3 behavioral changes were seen. The patient

4 continued to worsen in December, and new MRI

5 lesions were seen consistent with PML. The

6 natalizumab was stopped in mid-December, and in

7 February of the next year, 2005, JC virus was found

8 in his serum, in his spinal fluid, and also in

9 brain tissue. Avonex was stopped.

10 It is our understanding that the patient

11 continued to decline. He was treated with

12 Cytarabene, and he survived, but he is now

13 disabled.

14 [Slide.]

15 The third case is probably the most

16 complicated case to think about. This is a case of

17 a 60-year-old gentleman with Crohn's disease, and

18 he also passed away after taking a total of 8

19 natalizumab doses.

20 The subject was on natalizumab monotherapy

21 when his initial PML symptoms developed, and he had

22 a complicated history of intermittent concomitant

1 immunosuppressant use.

2 I will try to describe this to you  
3 briefly. You have the article in front of you, and  
4 you may read through it tonight. It's a little  
5 confusing to follow the time course.

6 He started azathioprine in 1998. You will  
7 remember he had Crohn's disease. He continued  
8 azathioprine until late 2002. This was eventually  
9 stopped because of immunosuppression. He had  
10 refractory anemia, low platelets.

11 He started natalizumab in March of 2002,  
12 and he received three doses at that time. Those  
13 three doses were given concomitantly with  
14 azathioprine. Then, the patient was randomized to  
15 receive placebo, so for some time he received  
16 placebo along with azathioprine.

17 He received placebo for approximately nine  
18 months and then the azathioprine was stopped late  
19 in the year of 2002, but he was still on placebo.  
20 Then, natalizumab was restarted in February of  
21 2003, and he received five doses from approximately  
22 February to June of 2003.

1           He was admitted with symptoms in July, and  
2   he declined physically, and eventually, he had a  
3   brain biopsy that was diagnosed as astrocytoma. As  
4   you know, this patient was eventually found on  
5   retrospective analysis to have PML.

6           When the company went back and examined  
7   the pathology in the brain, they did find positive  
8   JC virus in the brain pathology. This patient is  
9   also an interesting case study because he is the  
10   only patient out of the three who, when they looked  
11   back in time, at banked serum samples, they found  
12   that his JC virus in his blood was positive in May  
13   of 2003. That is two months before he became  
14   symptomatic, a low number of copies, but the number  
15   increased in July.

16           [Slide.]

17           So, I am going to stop there with the  
18   cases and I am going to talk about the safety  
19   analysis that was done. The company has given you a  
20   detailed description of the safety analysis that  
21   was performed, and I should say, as a division, we  
22   reviewed their analysis and we reviewed the results

1 under the IND, and were satisfied that they had  
2 conducted an adequate review, and do not feel that  
3 there are any lurking cases of PML that we have  
4 missed.

5 One piece of information that we requested  
6 that I thought I would share with you, this came in  
7 under the IND. We asked them, of the patients, when  
8 you went back, of all the folks who had received  
9 natalizumab, that you went back and tested looking  
10 for more cases, we wondered how many doses had  
11 those people received.

12 So, this is just a breakdown, this chart,  
13 and as you can tell, I have split it into the MS  
14 safety trial and then Crohn's disease and  
15 rheumatoid arthritis safety trial.

16 In the MS safety trial, you can see quite  
17 a few of the patients had received, there were a  
18 total of 1,869, and over half had received 24 or  
19 more doses.

20 In the Crohn's disease and rheumatoid  
21 arthritis trial, more patients had received less  
22 than 12. The greatest percentage was less than 12

1 doses.

2 [Slide.]

3 I will summarize PML. As you know, there  
4 are only three cases identified. Again, we find  
5 that after review of their study, we think that  
6 their analysis that was done was adequate, and we  
7 don't think there are any other cases that we have  
8 missed. We have not been able to identify  
9 additional risk factors.

10 Most importantly, the relationship between  
11 concomitant immunosuppression and PML is unclear.  
12 I know that there has been a lot of talk in the  
13 neurology community about decreasing the risk of  
14 PML with monotherapy use, and as an agency, we do  
15 not feel comfortable in saying that you are  
16 decreasing your use with monotherapy, because we  
17 feel as though we don't have enough information to  
18 really tell patients that and give them that  
19 confidence.

20 So, we are in quite a conundrum and we are  
21 hoping that the committee will be able to help us.  
22 As you delve into this, you realize that there are

1 only three cases, and it is hard to draw a lot of  
2 conclusions when you only have three cases.

3           However, to get more data, you essentially  
4 have to expose more patients to natalizumab, and so  
5 how to do that, if we should do that and how we  
6 should do that, that is really where we are seeking  
7 your guidance.

8           I am going to stop here and I guess I will  
9 take clarification questions and then Dr. Hughes  
10 will come up to the microphone.

11           DR. KIEBURTZ: Dr. McArthur.

12           DR. MCARTHUR: Dr. McDermott, in the first  
13 case, the woman, the 46-year-old woman with  
14 multiple sclerosis, the autopsy findings were  
15 overwhelmingly consistent with PML, but were there  
16 any autopsy findings of multiple sclerosis?

17           DR. McDERMOTT: I have not seen the  
18 autopsy report. You may be alluding to an article  
19 that was recently published that suggested that the  
20 patient did not have MS, and I don't think that I  
21 can comment on that. I haven't seen the autopsy  
22 report. I don't have any basis to tell you one way

1 or another.

2 Let me go back. I missed the most  
3 important slide, my acknowledgment slide. I  
4 apologize to my colleagues. The review team is a  
5 very large team, and if I listed every person on  
6 the review team, I would have to pass out  
7 binoculars to the committee.

8 Our next speaker is Dr. Hughes, and she is  
9 going to talk to you about safety.

10 Safety

11 DR. A. HUGHES: Hi. Thank you very much.

12 [Slide.]

13 In this talk, I am going to discuss our  
14 view of the major safety concerns associated with  
15 natalizumab outside of PML. My goal is to allow  
16 you to consider natalizumab's risk-benefit profile  
17 more fully as you consider the questions that we  
18 have posed to you.

19 [Slide.]

20 I will focus here on just three major  
21 safety issues. First, infections, again, my  
22 discussion is limited entirely to infections other

1 than PML. Second, immunogenicity and  
2 hypersensitivity reactions, which Dr. McDermott has  
3 talked a little bit about in her presentation.  
4 Third, carcinogenicity.

5 My focus on these three concerns is driven  
6 both by the serious adverse events that were  
7 observed in the clinical trial development program,  
8 as well as by theoretical concerns based on  
9 natalizumab's mechanism of action. There is, of  
10 course, an overlap between these two things, but  
11 not a complete overlap.

12 In addition to discussing these three  
13 major safety issues in the context of the  
14 natalizumab clinical trial program, I will, if time  
15 allows, briefly review serious adverse events that  
16 were reported in the brief post-marketing interval.

17 [Slide.]

18 So, the first issue that I am going to  
19 talk about is infections, and just as natalizumab  
20 blocks the migration of leukocytes to sites of  
21 inflammation in the central nervous system, it may  
22 also impair the recruitment of lymphocytes and

1 monocytes to sites of infection.

2           You have heard a lot already about  
3 natalizumab and infections from the sponsor. I  
4 will present data regarding infections in a  
5 slightly different way than you saw it presented in  
6 Dr. Panzara's presentation, that I think is also  
7 useful to consider.

8           In clinical trial, cases that appear to  
9 represent the same type of infection were often  
10 categorized under numerous umbrella terms, and  
11 these distinctions were often helpful, but  
12 sometimes probably not clinically meaningful.

13           For example, an upper respiratory tract  
14 infection might be classified as upper respiratory  
15 tract infection not otherwise specified,  
16 nasopharyngitis, or pharyngitis viral not otherwise  
17 specified, to name just a few of the many terms  
18 denoting upper respiratory tract infections.

19           So, I will consider cases of upper  
20 respiratory tract infections together, as well as  
21 cases of all lower respiratory tract infections  
22 together, as well as all cases of gastroenteritis

1 and vaginal infections to give you a better  
2 understanding, I hope, of the incidences of these  
3 infections.

4 So, after this long preamble, in  
5 placebo-controlled multiple sclerosis studies,  
6 natalizumab and placebo-treated patients had  
7 similar incidences of infections overall and  
8 serious infections.

9 Incidences of upper respiratory tract  
10 infections, which I just talked a lot about, were  
11 similar, as you can see. Incidences of urinary  
12 tract infections, both overall and serious, were  
13 similar in natalizumab and placebo-treated  
14 patients, and this is a safety concern with data  
15 through one year, but it wasn't borne out with the  
16 two-year data.

17 Incidences of gastroenteritis were  
18 similar. That was another concern based on data  
19 just through one year.

20 [Slide.]

21 Infections in which there was a slightly  
22 greater degree of difference between natalizumab

1 and placebo-treated patients in incidence, as you  
2 can see on this slide, were all lower respiratory  
3 tract infections, 13.3 percent of  
4 natalizumab-treated patients had infections  
5 categorized as any type of lower respiratory tract  
6 infections, compared to 12.2 percent of  
7 placebo-treated patients.

8 0.4 percent of patients treated with  
9 natalizumab had serious pneumonias, and this is  
10 compared to 0.2 percent of placebo-treated  
11 patients.

12 I would like to point out again that  
13 natalizumab-treated patients had a slightly higher  
14 incidence of herpes infections compared to  
15 placebo-treated patients, 7 percent compared to  
16 about 6 percent.

17 In terms of atypical infections--and I use  
18 this term on purpose rather than opportunistic  
19 infections--there was one case of cryptosporidial  
20 gastroenteritis in the monotherapy Study 1801.

21 This case is interesting in that  
22 cryptosporidial gastroenteritis can occur in

1 immunocompetent patients, but usually resolved in a  
2 couple of weeks without treatment. This patient,  
3 who was otherwise healthy, 31 years old, again not  
4 on concomitant Avonex, developed diarrhea after the  
5 17th natalizumab infusion, and it didn't resolve  
6 for about 70 days.

7           There was also an acute CMV infection with  
8 transaminitis in the open-label Study 1808. This,  
9 though, is a typical presentation of an acute CMV  
10 infection in an immunocompetent patient.

11           [Slide.]

12           Turning to Crohn's disease studies, there  
13 was a similar incidence of serious infections in  
14 placebo-controlled Crohn's disease studies, 2.5  
15 percent versus 2.6 percent, but there was a  
16 slightly increased incidence of infections overall  
17 in the natalizumab-treated patients compared to the  
18 placebo-treated patients, as you can see, 40  
19 percent versus 36 percent.

20           As listed, the incidences of selected  
21 infections on this slide, you can see that in the  
22 Crohn's disease studies, there was an increased

1 incidence of upper respiratory tract infections,  
2 but not lower respiratory tract infections in  
3 natalizumab-treated patients.

4           On this slide, I would like to note that  
5 herpes infections occurred in 1.6 percent of  
6 natalizumab-treated patients compared to 1 percent  
7 of placebo-treated patients.

8           I should point out here that the  
9 placebo-controlled Crohn's disease studies were  
10 much shorter. Patients received from just 1 to 3  
11 natalizumab infusions.

12           There were two cases of serious viral  
13 meningitis in natalizumab-treated patients in these  
14 short-term, acute treatment, placebo-controlled  
15 Crohn's disease trials, no cases in the  
16 placebo-treated group.

17           These cases were fairly typical for viral  
18 meningitis although they were serious adverse  
19 events and the patients were hospitalized.

20           There were two serious UTIs in  
21 natalizumab-treated patients, none in  
22 placebo-treated patients in the placebo-controlled

1 Crohn's disease studies. Again, this is  
2 considering all UTIs together.

3 In the short-term, placebo-controlled  
4 Crohn's disease studies, there was one serious CMV  
5 infection, a case of CMV colitis. The patient was  
6 also receiving azathioprine.

7 [Slide.]

8 In long-term Crohn's disease studies, that  
9 is where we saw the atypical infections, as the  
10 sponsor noted. There were six serious atypical  
11 lower respiratory tract infections, and I call  
12 these infections atypical either because of the  
13 passage it involved or because of the features of  
14 the case, such as the pneumonia with lung abscess,  
15 a pathogen was never identified in that case.

16 There was a case of pulmonary  
17 aspergillosis, a case of pneumocystis pneumonia, a  
18 case of varicella pneumonia, a case of  
19 mycobacterium avium intracellulare complex  
20 pneumonia, and a case of Burkholderia cepacia  
21 infection, which is a concern in cystic fibrosis  
22 patients, generally not seen or very, very rarely

1 seen in immunocompetent patients.

2 I should mention that of these six cases,  
3 two of the patients were not on any  
4 immunosuppressive medications or any other  
5 immunomodulatory medications. The rest of the  
6 patients, though, were on corticosteroids or  
7 azathioprine, or a combination of those two.

8 I would also like to note that these  
9 infections occurred after varying numbers of  
10 natalizumab infusions, ranging from 3 to 34, and  
11 there was not a clear relationship between the  
12 number of natalizumab infusions and the risk for  
13 atypical infections although that is certainly  
14 based on a very small number of cases or infections  
15 overall, as the sponsor pointed out.

16 There was a case of possible tuberculosis  
17 infection, which you heard about. This is an  
18 interesting case, and based on the information that  
19 we have, I don't think is terribly compelling for  
20 being a TB infection, although it is certainly  
21 concerning with a product like natalizumab.

22 It was a patient who after receiving 22

1 infusions, two and a half months later--and I  
2 should note he had a history of multiple prednisone  
3 courses, and was also taking azathioprine and had  
4 been on that drug for a year and a half--about two  
5 and a half months after 22 natalizumab infusions,  
6 he had surgery for Crohn's disease flare.

7 A couple of months later, he had an  
8 ileostomy takedown, and at that time it was noted  
9 that his peritoneum was studded with granulomas,  
10 and the pathology revealed granulomatous  
11 inflammation with confluent caseous necrosis, and,  
12 of course, Crohn's disease is associated with  
13 non-caseating granulomas, so it was thought to be  
14 representative of a tuberculosis infection, but AFB  
15 staining and PCR testing for mycobacterial DNA were  
16 negative.

17 [Slide.]

18 In terms of immunogenicity, which is the  
19 second major safety concern that I am going to turn  
20 to, treatment with therapeutic proteins can lead to  
21 the formation of antibodies against the product,  
22 and that is why we considered this as a major

1 safety concern, and why the sponsor monitored  
2 anti-natalizumab antibody formation every 12 weeks  
3 in the Phase III multiple sclerosis studies and in  
4 selected Crohn's disease studies, as well.

5 Ten percent of patients had a positive  
6 antibody titer at least once. I should mention  
7 that anti-natalizumab antibody formation is of  
8 great interest because it is associated with  
9 potentially hypersensitivity reactions, decreased  
10 efficacy, and potentially other adverse events.

11 So, getting back to the incidence  
12 formation, 10 percent of patients has a positive  
13 antibody titer at least once. As Dr. McDermott  
14 mentioned, 6 percent of those patients were  
15 persistently positive, so they had at least two  
16 positive antibody titers.

17 Four percent of patients were transiently  
18 positive meaning they were positive once, or they  
19 were positive on their last assessment.

20 The incidence of anti-natalizumab antibody  
21 formation was higher in Study 1802. It was 12  
22 percent compared to Study 1801, and it was 9

1 percent. Actually, I take back what I just said.  
2 The patients who were positive on their last  
3 assessment and weren't followed up again, I believe  
4 those patients were characterized as being  
5 persistently positive.

6 Now, there is a concern, a historical  
7 concern with therapeutic proteins that  
8 intermittent, irregular infusions may lead to a  
9 higher incidence of antibody formation against the  
10 product. We don't have enough information from the  
11 natalizumab trials about whether intermittent,  
12 irregular infusions, so not monthly, could lead to  
13 a higher incidence of antibody formation than was  
14 seen generally, about 10 percent.

15 These was a study, Study 251, a Crohn's  
16 disease study, in which patients were dosed when  
17 they had flares, and that study has the potential  
18 to give us some information about this issue, but  
19 the numbers are really too small to draw any  
20 conclusions about them.

21 [Slide.]

22 Anti-natalizumab antibody formation was

1 strongly associated with infusion reactions and  
2 hypersensitivity reactions.

3           Infusion reactions occurred in 77 percent  
4 of persistently antibody-positive patients. Again,  
5 infusion reactions were defined as adverse events  
6 that occurred within two hours of the start of the  
7 natalizumab infusion.

8           So, they occurred in 77 percent of  
9 persistently positive antibody-positive patients  
10 compared to 20 percent of antibody-negative  
11 patients and 29 percent of transiently  
12 antibody-positive patients.

13           So, the profile of the transiently  
14 positive patients was actually very close to the  
15 profile of the antibody-negative patients. It was  
16 really the persistently antibody-positive patients  
17 that stood out in terms of the infusion reactions  
18 and the increased multiple sclerosis relapses,  
19 which I will talk about in the next slide.

20           Anaphylactic reactions very notably  
21 occurred in 5.3 percent of antibody-positive  
22 patients in the Studies 1801 and 1802, in which

1 anti-natalizumab antibody formation was assessed,  
2 and it occurred in no patients who were  
3 antibody-negative throughout these studies.

4 In the Crohn's disease studies, which  
5 again were much shorter, anaphylactic reactions  
6 occurred in 1.3 percent of antibody-positive  
7 patients, and again in no antibody-negative  
8 patients.

9 [Slide.]

10 Multiple sclerosis relapses and also  
11 Crohn's disease exacerbations were reported more  
12 frequently as adverse events in antibody-positive  
13 patients compared both to transiently positive  
14 patients and antibody-negative patients.

15 Again, this is just adverse events that  
16 were reported, not relapse defined by any  
17 meaningful criteria. Fifty-seven percent of  
18 antibody-positive patients had adverse events of  
19 multiple sclerosis relapse compared to 35 percent  
20 of antibody-negative patients.

21 The incidence of infections,  
22 interestingly, was lower in persistently

1   antibody-positive patients compared to  
2   antibody-negative patients.

3           Overall, infections were reported in 69  
4   percent of persistently antibody-positive patients  
5   compared to 82 percent of antibody-negative  
6   patients. This pattern was seen for many of the  
7   individual infections, as well.

8           Just to select herpes infections, which  
9   are of concern to us, they were observed--and this  
10   is simplex and zoster, all herpes infections--they  
11   were observed in 2.7 percent of persistently  
12   antibody-positive patients compared to 8.4 percent  
13   of antibody-negative patients, and this is in the  
14   two pivotal studies, 1801 and 1802.

15           [Slide.]

16           Just briefly to talk about the overall  
17   population of patients, again not getting away from  
18   antibody-positive versus antibody-negative  
19   patients, anaphylactic reactions were observed in  
20   multiple sclerosis placebo-controlled studies in  
21   0.4 percent of patients treated with natalizumab  
22   compared to 0.2 percent of patients treated with

1 placebo.

2 In the shorter Crohn's disease  
3 placebo-controlled studies, there was one  
4 anaphylactic reaction in a placebo-controlled  
5 study. In long-term studies, there was one  
6 additional case of anaphylaxis.

7 This case is interesting. The patient had  
8 received four infusions in a prior study, had an  
9 interval of 300 days before receiving his first  
10 infusion in Crohn's Disease Study 251, and had an  
11 anaphylactic reaction. This is interesting to us  
12 because of the theoretical possibility that the  
13 antibody formation might be higher in patients who  
14 are not dosed regularly.

15 I have talked a lot about or some about  
16 anaphylactic reactions. I should mention that skin  
17 and subcutaneous tissue disorder reactions were  
18 actually the most common hypersensitivity infusion  
19 reactions in the multiple sclerosis studies.

20 They occurred in 4.6 percent of the  
21 natalizumab-treated patients compared to 2.2  
22 percent of the placebo-treated patients. Of the

1 reactions categorized under the broad umbrella of  
2 the skin and subcutaneous tissue disorder infusion  
3 reactions, urticaria was the most common, 1.6  
4 percent of patients in the MS studies who were  
5 treated with natalizumab had urticaria compared to  
6 0.3 percent of patients treated with placebo.

7 Per protocol, those patients had to  
8 discontinue from the trial.

9 There were a few delayed hypersensitivity  
10 events. Events reported as serum sickness in  
11 multiple sclerosis studies were actually balanced  
12 in the natalizumab and placebo treated groups.  
13 There was also, in the Crohn's disease studies, a  
14 case reported as a Type 4 hypersensitivity  
15 reaction, and there was one case of leukocytic  
16 classic vasculitis.

17 Most hypersensitivity events occurred  
18 during or immediately after the second infusion,  
19 but some occurred later. One case of anaphylaxis  
20 occurred in association with the 13th infusion.

21 I should mention now, this wasn't observed  
22 in the clinical trial setting, but in case I don't

1 have time to talk about it when I talk about  
2 post-marketing events, there were some events  
3 reported in the serious hypersensitivity events  
4 reported in the post-marketing setting in  
5 association with the first natalizumab infusion.  
6 That was not observed in the clinical trial  
7 setting.

8 [Slide.]

9 The third and final major safety issue I  
10 am going to discuss today is carcinogenicity, and  
11 that is a concern, more a theoretical concern at  
12 this point. Tumor immunosurveillance is mediated  
13 by T-lymphocytes because natalizumab interferes  
14 with their trafficking. We are concerned that it  
15 has the potential to increase the risk of cancer.

16 In the multiple sclerosis  
17 placebo-controlled studies, malignancies were  
18 balanced in natalizumab and placebo-treated  
19 patients. I have listed on this slide the types of  
20 malignancies that were observed just in  
21 natalizumab-treated patients.

22 You can see there were no cases of

1 leukemia or lymphoma, no particularly unusual types  
2 or patterns of malignancies. In Crohn's disease  
3 studies, malignancies were more frequently reported  
4 in the natalizumab group compared to the placebo  
5 group, 0.6 percent versus 0.2 percent, but as you  
6 will remember, the number of infusions the patients  
7 received was small. Biological plausibility I  
8 think is quite low.

9 [Slide.]

10 I have listed again the types of neoplasms  
11 observed in natalizumab-treated patients. In the  
12 Crohn's disease studies, I listed all neoplasms on  
13 this slide rather than just malignancies.

14 I thought it was of note that a meningioma  
15 and a craniopharyngioma were picked up during the  
16 dose suspension safety evaluation study when all  
17 patients were assessed to see if there were any  
18 additional cases of PML.

19 Now, I have saved the most concerning case  
20 potentially, I have listed it last. There was one  
21 case of a lymphoma, and this is the only case of a  
22 leukemia or lymphoma that has been observed in all

1 the clinical trials, and basically, in all patients  
2 treated with natalizumab, there were no leukemias  
3 or lymphomas observed in the post-marketing  
4 setting, the brief post-marketing setting.

5 [Slide.]

6 Just a little bit about this case. It was  
7 a 49-year-old man who had received six infusions of  
8 natalizumab in the course of two Crohn's disease  
9 studies, from September 2004 to February 2005.

10 On his screening examination in September  
11 of 2004, it was noted that he had submandibular  
12 lymphadenopathy. Subsequent examinations, though,  
13 this lymphadenopathy wasn't noted.

14 He had a history of infliximab therapy.  
15 He had received eight doses, and he was taking  
16 6-mercaptopurine at the time that he was taking  
17 natalizumab.

18 In August of 2005, he presented with  
19 enlarging lymph nodes that were painful, and he was  
20 diagnosed with a B-cell lymphoma. He had a CT and  
21 a biopsy that established this diagnosis. The  
22 histological type, though, is not known to us. At

1 this point, clinical details beyond what I have  
2 told you are pending on this case.

3 [Slide.]

4 I think that I have a minute to talk about  
5 serious adverse events that were reported in the  
6 post-marketing setting.

7 Primarily, I want to emphasize the two  
8 cases of herpes central nervous system infections  
9 that were reported. These are concerning to us  
10 particularly because of our concerns about  
11 cell-mediated immune compromise and because  
12 consistently, although the incidence difference was  
13 small, we observed an increase in herpes infections  
14 in the placebo-controlled trials in  
15 natalizumab-treated patients in both the MS and the  
16 Crohn's disease trials.

17 So, there were two herpes central nervous  
18 system infections. One case of herpes, HSV-2  
19 encephalitis, and the patient died. It was a  
20 patient with secondary progressive MS who had a  
21 history of methotrexate therapy lifetime and  
22 Novantrone therapy, actually had received a

1 lifetime maximum dose. Had one infusion of  
2 natalizumab, had viral symptoms.

3 Three months later, presented with  
4 seizures, was diagnosed as HSV-2 encephalitis by  
5 the appropriate CSF studies. Acyclovir was  
6 initiated, but the patient died the next day. The  
7 temporal relationship in this case is not typical  
8 certainly given that there was a three-month  
9 interval.

10 The temporal relationship in the second  
11 case is also a little bit interesting. This was a  
12 patient, a healthier patient, not on any other  
13 immunosuppressive medications, who was diagnosed  
14 with herpes meningitis basically right after  
15 receiving her first natalizumab infusion.

16 She had a history of migraine headaches,  
17 received natalizumab dose I believe in the morning,  
18 later that day had a headache, thought it was her  
19 usual migraine, but it didn't get better with her  
20 usual treatment.

21 Two days later she was admitted, diagnosed  
22 with herpes meningitis, but she recovered and did

1 well with appropriate treatment.

2 In terms of the malignancies that were  
3 reported in the post-marketing setting, again, no  
4 leukemias and lymphomas, which is an important  
5 point. There was a case of ovarian cancer, a case  
6 of endometrial cancer, three cases of skin cancer  
7 including one case of melanoma.

8 Hypersensitivity reactions and infections  
9 were the most commonly reported serious events, but  
10 they don't shed any more light on natalizumab's  
11 risk profile than the clinical trials did, so I am  
12 not going to discuss those cases any further.

13 [Slide.]

14 I would like to summarize briefly the  
15 three key safety issues starting with infections  
16 other than progressive multifocal  
17 leukoencephalopathy.

18 The types of infections that we observed  
19 suggest the possibility of a compromise in  
20 cell-mediated immunity. The herpes infections, the  
21 lower respiratory tract infections that were  
22 observed in both the multiple sclerosis trials,

1 although there weren't atypical pathogens, there  
2 was an increased risk of all lower respiratory  
3 tract infections and serious pneumonias, and, of  
4 course, the atypical lower respiratory tract  
5 infections that were observed in the Crohn's  
6 disease trials are of concern to us, and the cases  
7 of viral meningitis that were observed.

8           The role of concomitant medications and  
9 intercurrent illnesses in the pathogenesis of these  
10 infections is unclear, and, of course, that's the  
11 huge and difficult question before us.

12           I would like to mention on the summary,  
13 this summary slide, that the relative risk for  
14 infections was similar with monotherapy and  
15 combination therapy. In the combination therapy  
16 studies, patients tended to get more infections,  
17 but it was balanced in the natalizumab and placebo  
18 treatment groups.

19           As I mentioned, there was no clear  
20 association between increasing numbers of  
21 natalizumab infusions and the risk for infection.

22           [Slide.]

1           In terms of immunogenicity, antibody  
2   formation to anti-natalizumab occurred in  
3   approximately 10 percent of patients. Persistently  
4   positive antibodies were associated with infusion  
5   reactions, hypersensitivity reactions, increased  
6   multiple sclerosis relapses and Crohn's disease  
7   exacerbations, and a decreased incidence of  
8   infections supporting that natalizumab is  
9   associated with an increased risk for infections.

10           Anaphylactic reactions occurred in 0.4  
11   percent of natalizumab-treated patients with  
12   multiple sclerosis overall and in 5 percent of  
13   antibody-positive patients, a striking difference.

14           Hypersensitivity reactions were most  
15   common with the second infusion, but may occur  
16   much, much later.

17           [Slide.]

18           In terms of carcinogenicity, there was no  
19   evidence of an increase in risk for malignancies in  
20   the multiple sclerosis studies. There was one  
21   lymphoma observed in a patient who participated in  
22   a long-term Crohn's disease trial. It should be

1 noted he was also on 6-mercaptopurine and had a  
2 history of infliximab therapy. Those medications  
3 are associated with an increased incidence of  
4 malignancies themselves.

5           There have been no leukemias observed in  
6 the clinical trial setting or the post-marketing  
7 setting, but this is really the key point in terms  
8 of carcinogenicity, and it's a fairly obvious one,  
9 but I think it is worth making, that longer  
10 exposures will be needed before the risk for  
11 malignancies can be adequately assessed.

12           So, this is something that we are going to  
13 have to keep our eye on in addition obviously, to  
14 infections and hypersensitivity reactions if there  
15 is market reintroduction of natalizumab.

16           [Slide.]

17           I would also like to acknowledge--I will  
18 say Tysabri for the first time in the  
19 presentation--the Tysabri Review Team. Everyone  
20 has contributed to my understanding of the safety  
21 profile, and I would just like to acknowledge  
22 everyone, and apologize to people I have left off

1 the slide.

2 And I would like to introduce our next  
3 speaker, Dr. Diane Wysowski from the FDA's Office  
4 of Drug Safety unless there are, first, points of  
5 clarification for me. I don't know if we have time  
6 for that .

7 DR. KIEBURTZ: Dr. Hughes.

8 DR. A. HUGHES: Yes.

9 DR. M. HUGHES: I have a question about  
10 mortality. As I understand it, there are two  
11 PML-related deaths, but I want to try and put that  
12 in the context of other mortality that was seen in  
13 the overall experience with this drug.

14 What I am not clear about is how many  
15 total deaths are we talking about amongst  
16 drug-exposed subjects, how many are related to  
17 other infections, non-PML, and are any of the  
18 deaths related or thought to be related to MS?

19 DR. A. HUGHES: I would like to answer  
20 this question, if I may, at my seat where I have my  
21 notes.

22 In the development program overall, the

1 clinical trial development program, there are 17  
2 deaths overall. Thirteen of them were on  
3 natalizumab-treated patients, the rest obviously  
4 were in placebo-treated patients. Five of those  
5 were in multiple sclerosis studies, six were in  
6 Crohn's disease studies, and two were in the  
7 rheumatoid arthritis studies.

8 In terms of causes of death, I can briefly  
9 run through them. There was one malignancy, a  
10 melanoma. There were four infections, the two  
11 cases of PML, the case of pulmonary aspergillosis,  
12 the case of pneumocystis pneumonia. There was also  
13 a suicide.

14 There was an acute myocardial infarction  
15 with left ventricular rupture, a case of accidental  
16 carbon dioxide asphyxiation, respiratory distress  
17 secondary to multiple sclerosis progression. This  
18 was in a 5-year-old girl who received natalizumab  
19 in a compassionate use study.

20 There was a case of severe Crohn's disease  
21 exacerbation with multi-organ system failure.  
22 There was a case of respiratory failure due to the

1 procedural complication that occurred after a  
2 central line insertion, and there was the case of  
3 end-stage rheumatic pulmonary disease.

4 That was in the trials. There were five  
5 deaths in the post-marketing setting through the  
6 safety cutoff date, one case of suicide, one case  
7 of ovarian cancer, the case of herpes encephalitis,  
8 a death due to a motor vehicle accident, and a  
9 urinary tract infection in a very sick patient with  
10 multiple sclerosis who had other medical problems,  
11 and that case was actually reported by a family  
12 member, and there aren't too many details about  
13 that.

14 DR. SEJVAR: Just a real quick question.  
15 The cases of viral meningitis, were they  
16 substantiated cases of viral meningitis, or was  
17 there the possibility of aseptic meningitis from  
18 the agent entertained?

19 DR. A. HUGHES: I believe that they were  
20 substantiated cases of viral meningitis although I  
21 will have to look. I will have to get back to you  
22 on that tomorrow.

1 MS. SITCOV: Are the number of deaths in  
2 these studies, 1801 and 1802, separate from the  
3 PML, are those high numbers for studies like this,  
4 or are these conservative numbers? I mean how many  
5 people die from these kinds of studies?

6 DR. A. HUGHES: Dr. Katz and others, and  
7 Dr. Walton may be able to give a better perspective  
8 on this than I can. I think it's fairly typical,  
9 but--do you have anything to add?

10 DR. WALTON: We were not impressed that  
11 the overall mortality rate was markedly different  
12 than we might expect in MS studies. Of course,  
13 different studies use different populations, so it  
14 is not possible to really compare the precise  
15 mortality rates, so we tend to focus more on the  
16 nature of the mortality, but the absolute rates did  
17 not strike us as notably different.

18 MS. SITCOV: So, you don't look at this  
19 and say it's striking.

20 DR. WALTON: No.

21 DR. A. HUGHES: I think that the fact that  
22 the deaths were not notably increased in

1   natalizumab-treated patients compared to  
2   placebo-treated patients is informative, and not  
3   for that question.

4                   Risk Minimization Action Plan

5           DR. WYSOWSKI: Good morning. My name is  
6   Diane Wysowski and I am an epidemiologist in the  
7   Division of Drug Risk Evaluation, Office of Drug  
8   Safety, FDA.

9           I am here to review and discuss the  
10   Tysabri Risk Minimization Action Plan submitted by  
11   the company sponsors Biogen Idec and Elan. The  
12   information presented is based on our understanding  
13   of several versions of the plan and on discussions  
14   between the sponsors and the FDA.

15           Some of the changes in the plan came in  
16   yesterday, and I will mention the changes that have  
17   been made although my slides have not been updated.

18           [Slide.]

19           In this presentation, I will review the  
20   main features of the plan including its goals, its  
21   methods, the Tysabri Registry that is primarily for  
22   PML surveillance and opportunistic infection

1 surveillance, and the Tysabri observational cohort  
2 study, and I will present issues and questions  
3 relating to each.

4 [Slide.]

5 First, I think it's worth considering the  
6 sponsors' goals for the Risk Minimization Action  
7 Plan. They are: To promote informed risk-benefit  
8 decisions about Tysabri use in the treatment of  
9 multiple sclerosis patients; to minimize the risk  
10 of PML by contraindicating Tysabri in  
11 immunocompromised patients, and by ensuring that  
12 physicians know that Tysabri is contraindicated in  
13 these patients; and to minimize the health  
14 consequences of PML including disability, and death  
15 through early diagnosis.

16 [Slide.]

17 The plan features the use of a Medication  
18 Guide provided by doctors for patients to read  
19 about Tysabri, the risk of PML, other safety  
20 concerns that the patients should know, and  
21 instructions on the importance of reporting new or  
22 continuously worsening neurological symptoms

1 lasting over several days.

2 It requires mandatory enrollment of  
3 prescribers and patients.

4 [Slide.]

5 The plan also requires a mandatory  
6 Patient-Physician Acknowledgment Form, similar to  
7 an informed consent form, that is to be completed  
8 and signed by the patient and the physician.

9 The forms and the Tysabri prescription are  
10 to be sent to Biogen Idec where the patient and  
11 prescriber information are entered into the Tysabri  
12 Registry.

13 [Slide.]

14 On the Patient-Physician Acknowledgment  
15 Form, the prescribing doctor acknowledges and signs  
16 that he or she has read the full prescribing  
17 information, is aware of the risk of PML including  
18 disability and death, has discussed the risks and  
19 benefits of Tysabri with the patient, is  
20 prescribing the product for relapsing multiple  
21 sclerosis, confirms that the patient has no  
22 contraindications including immunosuppression, has

1 told the patient to report any new or continuously  
2 worsening neurological symptoms lasting over  
3 several days, and is enrolling in the Tysabri  
4 Registry.

5 [Slide.]

6 Similarly, the patient acknowledges and  
7 signs that he or she has read the Medication Guide,  
8 is aware of Tysabri's PML risk that includes  
9 disability and death, has discussed the risks and  
10 benefits with the doctor, understands the  
11 importance of reporting to the doctor any new or  
12 continuously worsening neurological symptoms, and  
13 is enrolling in the Tysabri Registry.

14 [Slide.]

15 Following the receipt of the forms and the  
16 prescription, the sponsors plan to enter the  
17 patient and prescriber information into the Tysabri  
18 Registry, match the patient to a registered  
19 infusion center, notify the infusion center of  
20 patient authorization to receive Tysabri, and  
21 provide the infusion center with the patient  
22 authorization number.

1           The plan does not require that the patient  
2   be reassessed by the prescribing physician and  
3   reauthorized at regular intervals to receive  
4   Tysabri.

5           [Slide.]

6           Tysabri will be shipped from a centralized  
7   distribution system consisting of one distributor,  
8   and less than or equal to 12 specialty pharmacies.  
9   It will be sent only after the shipping company has  
10  received the patient authorization code from the  
11  company sponsors.

12          [Slide.]

13          Tysabri will be administered only at  
14  registered infusion centers that attest to  
15  compliance with the risk management program.  
16  Infusion centers can be a hospital clinic, a  
17  stand-alone clinic, or a doctor's office.

18          Biogen Idec and Elan estimate that 2,000  
19  infusion centers will be registered to administer  
20  Tysabri.

21          [Slide.]

22          Before Tysabri is administered, the

1 infusion center nurse is to confirm that the doctor  
2 and patient have been enrolled in the Tysabri  
3 Registry.

4           Using the patient checklist, the nurse  
5 also is to confirm that the patient has multiple  
6 sclerosis, has a copy of the Medication Guide and  
7 has read it, is not known to be immunocompromised  
8 by HIV, hematological cancers, organ transplants,  
9 and anti-neoplastic and immunosuppressive drugs,  
10 and that the patient has not experienced any new or  
11 continuously worsening neurological symptoms  
12 lasting over several days.

13           The checklist provides the following  
14 examples of the neurological symptoms that would  
15 require a hold on Tysabri administration: new or  
16 sudden decline in the patient's thinking, eyesight,  
17 balance, or strength.

18           Also, the nurse is to document Tysabri  
19 administration on an infusion log.

20           [Slide.]

21           Although there is contraindication of  
22 Tysabri, if the patient is immunocompromised, the

1 plan does not state whether Tysabri is  
2 contraindicated with concomitant or recent use of  
3 immunomodulators, such as interferon-beta, with the  
4 systemic corticosteroids, such as  
5 methylprednisolone, and with other steroid and  
6 immune suppressant drugs.

7 [Slide.]

8 Currently, the patient checklist that the  
9 infusion center nurse is to use to determine if the  
10 patient is immunocompromised includes only a few  
11 diseases and six drugs that can induce an  
12 immunocompromised state.

13 The six drugs currently named on the  
14 checklist are azathioprine, Cytosan, methotrexate,  
15 Novantrone, CellCept, and Rituxan, however, we note  
16 that the sponsors' focus group composed of doctors,  
17 patients, MS nurses, and infusion nurses, requested  
18 that all drugs and diseases that could induce an  
19 immunocompromised state be clearly spelled out.

20 [Slide.]

21 The sponsors also plan to provide ongoing  
22 educational information for physicians and infusion

1 center nurses that will be delivered via mailings,  
2 a website, a toll-free help line, and continuing  
3 medical education programs.

4 They will conduct a survey of physician  
5 prescribers and infusion center nurses about their  
6 knowledge of Tysabri's PML risk and appropriate use  
7 conditions.

8 [Slide.]

9 An important feature of the plan is the  
10 Tysabri Registry whereby all patients who receive  
11 Tysabri will be systematically followed for the  
12 development of PML and to determine the PML  
13 incidence rate.

14 Patients will also be followed for the  
15 development of serious opportunistic infections.

16 The sponsors plan to ask prescribing  
17 doctors every six months if the patient is  
18 continuing on Tysabri and if the patient has PML.  
19 They also will ask the physician if the patient has  
20 developed any serious opportunistic infections and  
21 if the patient has died from any cause.

22 The sponsors recently added that follow-up

1 patient deaths will be accomplished through the  
2 National Death Index with collection of death  
3 certificates from state health departments.

4 While the former version of the plan did  
5 not specify the length of patient follow-up after  
6 Tysabri discontinuation, the sponsors now state  
7 that the patient will remain in the registry for a  
8 minimum of six months after the last dose of  
9 Tysabri.

10 They also state that noncompliance with  
11 the requirements for patient follow-up would result  
12 in de-enrollment of the patient to receive Tysabri.

13 The plan does not specify if the Tysabri  
14 Registry will contain a dosing history for all  
15 individuals who receive the drug in the clinical  
16 trials and in the previous post-marketing period.

17 Adding dosing history to the Tysabri  
18 Registry would enable the prescriber, the patient,  
19 the infusion nurse, and the registry to track the  
20 cumulative number of doses the patient has  
21 received, and would be important for clinical and  
22 risk assessment purposes.

1 [Slide.]

2 The sponsors plan special assessment of  
3 suspected PML cases for early diagnosis of PML.  
4 This would include administering a PML specific  
5 questionnaire, obtaining clinical details, and  
6 confirming the diagnosis based on an MRI and  
7 cerebrospinal fluid, JC virus testing.

8 For uncertain diagnoses, they plan to  
9 submit the data to an external PML expert. The  
10 sponsors will report confirmed cases to FDA within  
11 15 days of receipt. On a quarterly basis, they  
12 plan to provide to FDA the PML incidence rate and a  
13 qualitative analysis of risk factors.

14 [Slide.]

15 We have the following questions for the  
16 Advisory Committee which are simplified versions of  
17 the questions they will be asked to answer.

18 To maximize the benefit and minimize the  
19 risk of Tysabri, should there be restriction of  
20 Tysabri by MS disability severity? Should there be  
21 restriction of Tysabri to patients who experience  
22 failure of other MS therapies?

1 [Slide.]

2 To minimize the risk of PML, should  
3 Tysabri be contraindicated with concomitant or  
4 recent use of the immune modulator drugs, systemic  
5 corticosteroids, and immune suppressant drugs?

6 [Slide.]

7 Regarding patient assessment, should  
8 prescribing physicians reassess and reauthorize  
9 patients on a periodic basis to receive Tysabri?  
10 If so, how frequently should this be done?

11 Along these lines, should the assessment  
12 of neurological symptoms and patient  
13 immunocompromise before Tysabri administration be  
14 performed by an infusion center nurse or by a  
15 doctor? Is this an assessment that a nurse should  
16 make?

17 Should the patient checklist include a  
18 longer, more comprehensive list of diseases and  
19 drugs that are known to induce an immunocompromised  
20 state?

21 [Slide.]

22 Concerning tracking of Tysabri use, should

1 there be one-to-one patient to vial distribution,  
2 such that each vial is associated with an  
3 individual patient for tight control of Tysabri  
4 distribution and tracking?

5 [Slide.]

6 Concerning follow-up of patients, would  
7 patient follow-up be aided by collection in  
8 real-time of Tysabri administration,  
9 discontinuation, and reasons for discontinuation?

10 As mentioned earlier, the sponsors  
11 recently added follow-up of patient deaths through  
12 the National Death Index and collection of death  
13 certificates from the state health departments.

14 This should aid collection of information  
15 on patients who have discontinued Tysabri and are  
16 lost to follow-up. However, we note that the  
17 National Death Index has an important limitation in  
18 that there is a lag time in getting deaths into the  
19 National Death Index.

20 [Slide.]

21 For the Tysabri observational cohort  
22 study, Biogen Idec and Elan plan to enroll 5,000 MS

1 patients from the Tysabri Registry in the United  
2 States and Europe, including 3,000 U.S. patients.  
3 They will follow patients for up to five years  
4 after the Tysabri start date.

5 The companies plan to assess the incidence  
6 and nature of all serious adverse events including  
7 serious infections and malignancies. The study  
8 will also help them investigate potential signals  
9 of unanticipated adverse events.

10 The study will collect information on  
11 concomitant immunomodulator and immunosuppressant  
12 therapies.

13 [Slide.]

14 We have the following comments about this  
15 study. Regarding ascertainment of deaths and  
16 causes, we think that the National Death Index  
17 should help identify deaths in the cohort, and this  
18 will be especially useful for patients who have  
19 discontinued Tysabri use or are lost to follow-up.

20 Following the NDI search, death  
21 certificates would need to be collected from state  
22 health departments.

1           We believe that inclusion of all patients  
2   in the Tysabri Registry would provide complete  
3   ascertainment and avoid selection bias. If not all  
4   patients are included, the subset of patients to be  
5   included in the observational cohort study should  
6   be selected based on statistical survey sampling  
7   procedures.

8           The lack of a non-exposed MS control group  
9   could pose problems in the interpretation of  
10   etiology. If the companies need to rely on  
11   population controls, the outcomes of interest may  
12   not be available from population databases.

13          Also, the study does not specify if  
14   previous Tysabri exposure accumulated in the  
15   clinical trial and in the previous post-marketing  
16   period would be counted towards the five-year  
17   follow-up time.

18          Further, is five years sufficient time for  
19   follow-up?

20          [Slide.]

21          The most important issues and questions  
22   concerning the Tysabri Risk Minimization Action

1 Plan that I raised above have been rephrased as  
2 questions for the Advisory Committee.

3 If the committee votes to have Tysabri  
4 reintroduced to the United States market, we  
5 believe that the issues and questions outlined in  
6 this presentation should be carefully considered by  
7 the committee in an effort to maximize the benefits  
8 of Tysabri, while minimizing its PML risk.

9 [Slide.]

10 Finally, I want to acknowledge my  
11 colleagues in the FDA's Office of Drug Safety who  
12 participated in the review of this Risk  
13 Minimization Action Plan.

14 Thank you.

15 DR. KIEBURTZ: Thank you, Dr. Wysowski.

16 Questions from the committee? Dr.  
17 Goldstein.

18 Questions from Committee to FDA

19 DR. GOLDSTEIN: Dr. Hughes, you went  
20 through all these individual numbers. Have you  
21 synthesized these, can you give us like what the  
22 total rate is or frequency is of serious and

1 opportunistic infections combined in treatment  
2 versus control, because we have seen all of these  
3 things in pieces, and I don't know what the unique  
4 rates are?

5 DR. A. HUGHES: I can give you an idea, I  
6 believe, of serious infections. Well, I believe  
7 that serious infections in the multiple sclerosis  
8 and Crohn's disease studies were on the slides. I  
9 am not sure if this is exactly answering your  
10 question.

11 But in the multiple sclerosis  
12 placebo-controlled studies, 2.4 percent of the  
13 natalizumab-treated patients had serious infections  
14 categorized as serious, compared to 2.3 percent of  
15 placebo-treated patients.

16 Again, in the MS studies, there was only  
17 that one atypical infection, the cryptosporidial  
18 gastroenteritis, and then in the placebo-controlled  
19 Crohn's disease studies, again, very short, just 1  
20 to 3 infusions, serious infections occurred in 2.5  
21 percent of natalizumab-treated patients and 2.6  
22 percent of the placebo-treated patients.

1           So, that is overall. I could give you, if  
2   you are interested later, if there are any specific  
3   serious infections that you are interested in, I  
4   could give you the incidence differences.

5           DR. GOLDSTEIN: What I was interested in  
6   is what the combined rate was of opportunistic and  
7   serious infections, for example, the herpes that we  
8   are concerned about, other viral infections  
9   combined, and they may balance out, and that's  
10   fine. I am just not sure what the numbers are.

11          MS. A. HUGHES: In terms of the herpes  
12   infections, that's in the multiple sclerosis  
13   placebo-controlled studies, it was about 7 percent  
14   versus 6 percent, natalizumab versus placebo. In  
15   the Crohn's disease placebo-controlled studies, it  
16   was 1.6 percent versus 1.0 percent, and this is all  
17   herpes infections.

18          In terms of the opportunistic infections,  
19   there were--it sort of depends on your definition  
20   of opportunistic--there were those 7, I considered  
21   7 atypical infections, the 6 lower respiratory  
22   tract infections and the extra pulmonary TB

1 infection may or may not actually be tuberculosis.  
2 Those all occurred in the long-term Crohn's disease  
3 trials.

4 There was just the case of CMV colitis in  
5 the placebo-controlled trial. That was the only  
6 one. And in the long-term Crohn's disease trials,  
7 there were approximately 1,500 patients, so that's,  
8 you know, 7 divided by 1,500. Is that helpful? It  
9 doesn't look like it.

10 DR. GOLDSTEIN: Again, you just went down  
11 the list again. I just wanted to know what the  
12 bottom line total number was in the two groups.  
13 Maybe you can calculate it for me afterwards and  
14 give it to us later.

15 MS. A. HUGHES: That might be more  
16 efficient.

17 DR. GOLDSTEIN: That would be helpful.

18 MS. A. HUGHES: Thanks.

19 DR. GOLDSTEIN: Sorry.

20 DR. KIEBURTZ: Any further questions?

21 DR. M. HUGHES: I don't know if it's good  
22 sense in these sorts of programs if there is any

1 potential for off-label use in a RiskMAP program.

2 DR. KIEBURTZ: Again, in the risk  
3 minimization program?

4 DR. M. HUGHES: Well, as I understand it,  
5 the physician has to sign that their patient has  
6 relapsing- remitting MS, so if they are telling the  
7 truth, it would exclude all patients without.

8 DR. WALTON: It also depends upon how  
9 tightly written the RiskMAP is.

10 DR. COUCH: Will this RiskMAP program need  
11 to go through human subjects or be, for instance,  
12 in academic centers or in private centers? Is  
13 there going to be any anticipated need for doing  
14 that?

15 Secondly, from a legal standpoint, will  
16 the procedure of discussion with the patients who  
17 are signing the appropriate forms take care of the  
18 legal aspect of it, or is there an anticipation  
19 that the judicial aspect of this, somebody can  
20 always come back and say, well, my client developed  
21 PML and you are still going to be at risk  
22 regardless of what papers you signed.

1 DR. TEMPLE: This is not an investigation.

2 We will fight to the death to insist on that. It  
3 is part of how to use the drug safely, and you  
4 can't opt out of it, and will not go to IRBs.

5 DR. KIEBURTZ: So, it's not a research  
6 tool.

7 DR. TEMPLE: It is not a research tool.  
8 We religiously won't learn anything from it, and I  
9 am not sure we can comment on the law.

10 DR. KIEBURTZ: Issues of legal tort  
11 issues.

12 DR. TEMPLE: Can I make one comment that  
13 came up previously? How you write one of these  
14 things can determine how possible it is to use a  
15 drug off label, and that is one of the things you  
16 are going to be asked.

17 For example, the doctor could sign  
18 something that says I know this drug is indicated  
19 only for MS. Well, fine, you can know that and  
20 still prescribe it for something else. He could  
21 also be asked to say my patient has MS. That's a  
22 different level of assurance, and those are the

1 very things that you need to think about when you  
2 think about what to write.

3 DR. WYSOWSKI: I just had a comment about  
4 off-label use. If you track the vials and link  
5 them to a patient, you are less likely to have  
6 off-label use I think, because otherwise, you might  
7 have some stockpiling in the infusion center, in  
8 the doctor's office, or whatever, and then with  
9 that, unless that excess gets sent back to the  
10 company, then, there is always that possibility  
11 that it could be used off label.

12 But that is one point for the committee to  
13 consider is about tying the vial to the patient.

14 DR. KIEBURTZ: Dr. McArthur.

15 DR. McARTHUR: Could I ask you, Dr.  
16 Wysowski, have you reviewed the checklists that  
17 have been mentioned several times? I don't see  
18 them in the documentation.

19 DR. WYSOWSKI: Right. I have looked at  
20 the checklist, and as I mentioned in my  
21 presentation, there are only a few diseases that  
22 are on that checklist, and six drugs, and I think

1 it's important for the committee to consider  
2 whether there might be a more comprehensive list of  
3 immunosuppressive drugs and diseases.

4 DR. McARTHUR: How about the checklist for  
5 new or continuing neurological symptoms?

6 DR. WYSOWSKI: They are very nonspecific,  
7 change in eyesight, change in balance, new or  
8 sudden change in eyesight, balance, strength, and  
9 thinking. So, you know, I am not a neurologist. I  
10 would assume that that might produce a large number  
11 of potentially false positive suspected PML cases.

12 DR. KIEBURTZ: Dr. Sejvar.

13 DR. SEJVAR: Just to clarify for myself,  
14 so the idea of the use of the NDI would be to  
15 cross-reference these folks and do annual  
16 cross-referencing with all-cause, all death causes?

17 DR. WYSOWSKI: I am sorry. Could you  
18 repeat the question?

19 DR. SEJVAR: The use of the National Death  
20 Index, basically, you would be performing annual  
21 cross-referencing of these enrolled or registered  
22 patients with the all cause of death data, is that

1 correct?

2 DR. WYSOWSKI: Right. That is my  
3 understanding.

4 DR. TEMPLE: That would be for people they  
5 can't find in the ways they are going about finding  
6 them, right, or not?

7 DR. WYSOWSKI: In think initially, what  
8 you do is you run the index, you know, and compare  
9 it with all the cohort patients, and then later on,  
10 you know, subsequently, you would just include the  
11 ones that you can't find or that have been  
12 discontinued on Tysabri and lost to follow-up.

13 But there is that lag period, so it's  
14 not--I don't know exactly--can you speak to that,  
15 the lag period, do you know what it is now?

16 DR. SEJVAR: We do similar assessment for  
17 CJD, and it's about anywhere between two and three  
18 years.

19 DR. KIEBURTZ: Ms. Sitcov, please.

20 MS. SITCOV: I am wondering, it sounds  
21 like if this drug gets approved, PML is a  
22 possibility in terms of occurrence, but I am

1 wondering what sort of adverse reactions, both  
2 qualitative and quantitative, if Tysabri gets  
3 approved, would cause Tysabri to be removed from  
4 the market.

5 DR. WALTON: Are you asking for a nature  
6 of events or a frequency?

7 MS. SITCOV: Well, I guess what has to  
8 happen if Tysabri gets approved, do 20 people have  
9 to die from PML, or what has to happen?

10 DR. KIEBURTZ: That may be a tomorrow  
11 question.

12 MS. SITCOV: Okay.

13 DR. KIEBURTZ: Dr. McArthur.

14 DR. McARTHUR: Could I ask Dr. McDermott  
15 the experience with other risk management or  
16 minimization programs, you mentioned clozapine, or  
17 maybe it wasn't you?

18 DR. McDERMOTT: That wasn't me.

19 DR. WYSOWSKI: Claudia Kawolski [ph], who  
20 is the Scientific Coordinator for Risk Management  
21 Plans, could probably speak about, you know, what  
22 has happened with our--

1 DR. McARTHUR: Well, that was the  
2 question, what have we learned from the clozapine  
3 mandatory registration that we could apply to  
4 Tysabri.

5 DR. WYSOWSKI: Gerald Dal Pan, our office  
6 director--

7 DR. TEMPLE: Well, Rusty can add. We can  
8 say a few things about clozapine. Of course, each  
9 one of these is unique. For clozapine, you have to  
10 bring in a white count from the week before in  
11 order to get the next dose.

12 The result is that agranular cytositis is  
13 discovered much earlier than it ever was before,  
14 and the mortality from the agranular cytositis that  
15 is indeed seen is much lower than people expected,  
16 a couple of percent instead of the 10 percent that  
17 was anticipated.

18 In addition, the registry assures that no  
19 one who gets a white count problem ever gets the  
20 drug again. The registry has been used by all of  
21 the generic makers, as well as the original maker,  
22 and so on.

1           Now, to be fair, and not to overstate it,  
2   it's a fairly simple question that is being asked.  
3   It is just about white count, relatively simple,  
4   not so complicated. It's a simple lab test.

5           But I would say we feel quite good about  
6   that. There has been a gradual rollback of how  
7   frequently you have to have the test after you have  
8   been on the drug for a certain number of years,  
9   your chance of getting it decreases, so the  
10   frequency has dropped back.

11          There are other similar ones. There is a  
12   similar program for a drug called bosentan for  
13   pulmonary hypertension that Doug knows more about  
14   than I do. That one is designed to prevent  
15   pregnancy, so you have to bring in your pregnancy  
16   test and your test of liver function, because those  
17   are the two things you are worried about there.

18          There have been some pregnancies. That is  
19   not good, we think fewer than otherwise, and there  
20   hasn't been a fatality due to liver disease yet, a  
21   relatively low use drug, but each one sort of has  
22   to be looked at.

1           They vary in stringency, they vary in how  
2   much you have to say and do. Each one is sort of  
3   targeted, and that is why a lot of the questions  
4   tomorrow are going to be about how to target this  
5   one.

6           DR. KIEBURTZ: About the clozapine one,  
7   too, it was modified. I think that is another  
8   important thing. It existed and then was modified  
9   based on the initial results of that.

10          DR. TEMPLE: Yes, absolutely. The  
11   frequency of testing is modified if you have been  
12   on it, I forget, more than six months, more than a  
13   year, or whatever, based on observed data.

14          DR. KATZ: It is not just the frequency,  
15   but the criteria that serve for deciding what to do  
16   have actually altered it, as well, so many things  
17   about it have been changed over time based on the  
18   data that has been accruing.

19          DR. KIEBURTZ: Last question.

20          DR. JUNG: I think it is clear that  
21   neurologists use drugs off label frequently as part  
22   of our practice. Given the fact that there is a

1 change in the indication to remitting-relapsing MS,  
2 do you think that there is any need to clarify the  
3 diagnosis of remitting-relapsing MS?

4 That seems fairly elementary, but if the  
5 drug is released, will there be pressure on  
6 physicians by their patients to expand the  
7 definition of remitting-relapsing to patients with  
8 primary progressive or secondary progressive? All  
9 of us who take care of MS patients know that there  
10 is a lot of overlap there, and how do we clarify  
11 that?

12 DR. KIEBURTZ: I think that is a question  
13 to us to discuss tomorrow quite specifically in  
14 terms of the nature of the severity and the  
15 characteristic of the patients.

16 It looks like I said the last question,  
17 but I will take two more from Dr. Goldstein and  
18 then Dr. DeKosky, and then we will stop for lunch.

19 DR. GOLDSTEIN: Thanks. This may also be  
20 some information that needs to be gathered for us  
21 for tomorrow, but in the background information,  
22 one of the things that was talked about is the

1 dropout rate on other established therapies of 15  
2 to 20 percent dropout rate.

3           What I was interested in is what the  
4 dropout rate was in this clinical trial for people  
5 who were enrolled in the clinical trial as compared  
6 to the dropout rates in the other clinical trials  
7 where these other therapies have been used. Are we  
8 expecting a difference, or are the dropout rates  
9 going to be similar to one another?

10           The second thing again may require some  
11 looking into is one of the things that we are being  
12 asked to do is, well, what group, if it is going to  
13 be restricted, should we consider, and one is  
14 treatment failures.

15           So, what definition is going to be used  
16 for treatment failure, and is there any data aside  
17 from this combined data that we know about from  
18 1802 that switching the patient to this drug as  
19 compared to a different immunomodulatory drug  
20 results in further improvement.

21           DR. KIEBURTZ: Again, I think we are  
22 edging into tomorrow.

1 DR. GOLDSTEIN: No, this is for tomorrow,  
2 but they may need to get some data together to be  
3 able to address those, so I wanted to ask them now  
4 for tomorrow.

5 DR. KIEBURTZ: Thank you.

6 DR. WALTON: If I may respond in part to  
7 your first question about the dropout rates. I am  
8 sure it is in here somewhere, although I cannot  
9 find the page in the briefing document, but in the  
10 natalizumab studies, the dropout rates were  
11 relatively small.

12 There was very good follow-up on almost  
13 all patients, but that is not really I think the  
14 question that you are trying to get at. The  
15 question is what will be the experience in clinical  
16 practice.

17 I would be very wary about trying to reach  
18 insight into that question based upon the clinical  
19 trials. Clinical trials are so different, such  
20 different circumstances than clinical practice is.

21 It is clear to us from the clinical trials  
22 with the beta-interferons that there was a much

1 better sustained compliance, sustained use within  
2 the clinical trials for the beta-interferons than  
3 is reported to be the experience in clinical  
4 practice.

5 So, based on that, I would be very wary  
6 about trying to reach conclusions about what the  
7 clinical practice experience in the future will be.

8 DR. GOLDSTEIN: That is exactly what I was  
9 trying to get, and probably dropout rate wasn't  
10 maybe the best term to use. What I meant is drug  
11 treatment discontinuation rates, and as you  
12 correctly point out, looking at clinical practice  
13 compared to clinical trials are looking at apples  
14 and oranges, but again, as part of the background  
15 information, we were told that 15 to 20 percent of  
16 MS patients stopped these interferons or whatever  
17 during their clinical care.

18 So, the question was within the clinical  
19 trials that were done for these drugs, what was the  
20 drug discontinuation rate in those trials compared  
21 to this. That way, we at least have apples and  
22 apples to look at.

1 DR. KIEBURTZ: Dr. DeKosky.

2 DR. DeKOSKY: This may also be for  
3 tomorrow, but the issue of who gets this drug and  
4 how we define relapsing-remitting would also have  
5 to deal with a first episode of likely MS with or  
6 without a clinical history, as Dr. Jung talked  
7 about, of episodes that did not reach the attention  
8 of a physician, but were part of the history, as  
9 well as initial optic neuritis and suspicion that  
10 there are other lesions in CNS, and whether that  
11 would meet the criteria for relapsing-remitting.

12 DR. KIEBURTZ: Thank you.

13 Russ, you get the final word.

14 DR. KATZ: Maybe to address Dr.  
15 Goldstein's second question, if I understood it,  
16 which was what do we know about if you switch from  
17 one interferon to another interferon, what is the  
18 response compared to if you switch from an  
19 interferon to Tysabri, somebody can correct me if I  
20 am wrong, but I don't think there is any reliable  
21 data that speaks to that question.

22 DR. WALTON: We have no data about that

1 sort of a crossover.

2 DR. KIEBURTZ: That concludes this  
3 morning. I would remind open public hearing  
4 speakers to check in at the desk if you intend to  
5 speak. We will start the open public hearing  
6 promptly at 1 o'clock.

7 Let me just remind folks there will be a  
8 set period of time, so that it is fair and  
9 equitable. It looks like committee members can  
10 leave their things here.

11 [Whereupon, at 12:05 p.m., the proceedings  
12 were recessed, to be resumed at 1:00 p.m.]

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1 A F T E R N O O N P R O C E E D I N G S

2 [1:00 p.m.]

3 DR. KIEBURTZ: The schedule for this  
4 afternoon is slightly more flexible in the sense  
5 that we will take the break if and when it seems  
6 appropriate, the one of the few things I get to  
7 decide today.

8 Just to remind people that there are two  
9 forms of public comment, individual and group.  
10 Individuals have three minutes to speak, groups  
11 have five minutes to speak. When your time is up,  
12 someone somewhere in this room will turn off your  
13 microphone, so when the three minutes is up, you  
14 are done.

15 This may seem overly restrictive and  
16 harsh, but there are a number of people who are  
17 scheduled to speak, and it only strikes me as fair  
18 and equitable that everyone gets the same amount of  
19 time to speak, and I believe people knew about this  
20 in advance. So, we will stick with that plan.

21 Before the beginning of the open public  
22 hearing I need to read the following.

1           Both the Food and Drug Administration and  
2   the public believe in a transparent process for  
3   information gathering and decision-making. To  
4   ensure such transparency at the open public hearing  
5   session of the Advisory Committee meeting, the FDA  
6   believes that it is important to understand the  
7   context of an individual's presentation.

8           For this reason, the FDA encourages you,  
9   the open public hearing speaker, at the beginning  
10  of your written or oral statement, to advise the  
11  committee of any financial relationship that you  
12  may have with the sponsor, its product, and, if  
13  known, its direct competitors.

14          For example, this financial information  
15  may include the sponsor's payment of your travel,  
16  lodging, or other expenses in connection with your  
17  attendance at the meeting.

18          Likewise, the FDA encourages you at the  
19  beginning of your statement to advise the committee  
20  if you do not have any such financial  
21  relationships. If you choose not to address the  
22  issue of financial relationships at the beginning

1 of your statement, it will not preclude you from  
2 speaking.

3 That's the end of that. We will now  
4 commence with the open public hearing, which is in  
5 a particular order of speakers as per the slide.

6 The first is Jason Mark.

7 Open Public Hearing

8 MR. MARK: Good afternoon. My name is  
9 Jason Mark. Both myself and Alex McDonald, the next  
10 designated speaker, will be ceding our time to  
11 representatives of the family of Anita Smith.

12 MS. SMITH: Thank you for the opportunity  
13 to speak to you today. My name is Beth. Anita  
14 Smith was my mother.

15 I am here with my brother Jason and my  
16 father Walt. My father prepared his statement to  
17 read to you, however, this is a very emotional,  
18 difficult time for him, and he has asked me to read  
19 his statement on his behalf.

20 I am here to briefly tell you about my  
21 wife, Anita Smith. Many of you have read about  
22 Anita in medical journals and newspaper articles.

1 Anita died from PML caused by Tysabri. Tysabri was  
2 withdrawn from the market because of Anita's death.  
3 I lost my wife, my best friend in the whole world  
4 because of this drug. My children lost a mother  
5 they loved, who loved them dearly.

6 Before she took Tysabri, Anita worked full  
7 time. She was an active, fully functioning person.  
8 She was not disabled, she did not appear ill.  
9 Anita was basically fine.

10 Beginning in 2000, Anita was prescribed  
11 Avonex. It cost us \$1,000 a month. In 2002, we  
12 were told that if we participated in a study, Anita  
13 would receive Avonex and another drug, Tysabri,  
14 that we wouldn't have to pay for any of the  
15 treatment or medications.

16 We were told that Biogen would pick up the  
17 tab for us. We were never told that Tysabri could  
18 result in Anita's death. If we knew this, we would  
19 have happily stayed away from the study.

20 I understand that this meeting is to  
21 determine whether Tysabri should come back onto the  
22 market and whether clinical trials of Tysabri

1 should be permitted to resume beyond what has  
2 already been permitted.

3 I am here with Dr. Gregory Shoukimas from  
4 Boston who can speak to you about my wife's medical  
5 history better than I can. The one thing he cannot  
6 describe for you is how broken my family's heart is  
7 over ever having Tysabri enter our lives.

8 I ask that Dr. Shoukimas speak to you now.

9 DR. SHOUKIMAS: Good afternoon. My name  
10 is Dr. Gregory Shoukimas. I am a neuroradiologist  
11 and have been practicing for 20 years, and I am  
12 here at the request of the Smith family. I am not  
13 sponsored by Biogen, and I am not sponsored by any  
14 competitors.

15 I am here to address primarily the issue  
16 of the raw data, that is, the individual data that  
17 a patient presents with and was enrolled in the  
18 study, the Tysabri study. That is, how did Anita  
19 Smith present clinically, what was her  
20 symptomatology, what was her physical examination,  
21 and what tests aided in making the diagnosis of  
22 multiple sclerosis.

1           In the talks that you have heard this  
2 morning, it is assumed that Anita Smith had  
3 remitting-relapsing multiple sclerosis, and that  
4 has been called into question. I have no time to  
5 go into the details of her physical examination,  
6 but suffice as to say that her clinical  
7 symptomatology was benign, relatively benign, was  
8 not disabling, and certainly did not contribute to  
9 her disability scores.

10           Her physical examinations for the most  
11 part were normal. She showed very minimal signs of  
12 decreased leg strength, spasticity, and slight  
13 hyperreflexia.

14           In December of 2001, her physical  
15 examination was entirely normal. She had reported  
16 to her neurologist she was doing well, and she had  
17 normal muscle strength in all major muscle groups,  
18 but despite all this clinical information that was  
19 available, she was being considered by her  
20 neurologist for the Antegren or Tysabri study,  
21 which she was told would be starting shortly, that  
22 is, within three or four months.

1 I had the fortune of talking with the  
2 Smith family for about an hour, and it was related  
3 to me by Mr. Smith and his daughter, Beth, that  
4 from the time of her visit to enrollment in the  
5 study, that is, the time of her first visit to the  
6 neurologist to enroll in the study, she thought of  
7 her problem as an annoyance.

8 She worked, carried the laundry up and  
9 down stairs, clearly not indicative of a disabled  
10 patient. She didn't get worse, and she didn't get  
11 better. There was some indication that she had  
12 visual problems, but this was never tested formally  
13 with electrophysiology tests to confirm that she  
14 had optic neuritis.

15 Her magnetic resonance imaging study in  
16 1999, which I have reviewed, showed some  
17 nonspecific white matter changes, and, in fact,  
18 given her previous history of migraine, may have  
19 reflected previous migraine. The changes were  
20 nonspecific, and while demyelination was considered  
21 criteria for this, for the diagnosis of MS was not  
22 fulfilled.

1           She had a cerebrospinal fluid analysis,  
2    which was normal, including IgG assessment,  
3    oligoclonal bands were nonexistent, and had one  
4    lymphocyte, which is nonspecific.

5           Electrophysiology studies were not  
6    performed especially visual, evoked potentials,  
7    which would have been helpful in making the  
8    diagnosis of optic neuritis.

9           Her clinical examination, as briefly, very  
10   briefly detailed, but more fully talked about by  
11   Dr. Godec later today, showed that she did not  
12   really have two clinically symptomatic attacks and  
13   that her objective lesions were not clearly  
14   defined.

15          So, the question really is did Anita Smith  
16   have multiple sclerosis. The talks again have  
17   assumed that she had relapsing-remitting disease,  
18   but, in fact, this was not ever clearly  
19   established. If, in fact, it was present at all,  
20   it was mild and stable with minimal neurological  
21   manifestations, and any objective tests that might  
22   have been helpful were ignored.

1           These are the MRI scans, which were not  
2   available when the New England Journal of Medicine  
3   published its clinical pathological study detailing  
4   the effects of MS on Mrs. Smith, and the Tysabri  
5   results and the progressive multifocal  
6   leukoencephalopathy which ensued.

7           These were the lesions that were described  
8   as 9 lesions. These are two illustrative MRs.  
9   There is a lesion back here. These are not very  
10  typical of MS. They are nonspecific findings.

11          These are two patients that have MS,  
12  similar in presentation, a little bit more severe,  
13  more objectively defined disease, but these MR  
14  scans are clearly contributory. There are some  
15  lesions in the periventricular white matter, close  
16  to the cephalo-junction region. In the Annals of  
17  Neurology 2001, the McDonald criteria were  
18  published, and clearly defined how MRs should be  
19  interpreted with respect to MS. The MR scan that  
20  Mrs. Smith underwent did not meet that criteria.

21          After her enrollment with two potent  
22  immunosuppressant and modified immunomodified

1 drugs, she was a minimally symptomatic patient  
2 whose diagnosis was questionable, and yet she was  
3 given the drugs, and progressive multifocal  
4 leukoencephalopathy ensued, causing her demise.

5 The enrollment of Anita Smith into a  
6 clinical trial of these two drugs is almost  
7 incomprehensible and certainly raises grave ethical  
8 concerns about Biogen Idec's process of enrollment.

9 The FDA has already decided that new  
10 clinical trials can proceed with Tysabri. As we  
11 examine the enrollment process for Anita Smith, we  
12 must question and examine the serious concerns that  
13 Biogen Idec is incapable of proceeding in a safe  
14 manner with future clinical trials. Obviously, they  
15 admitted, enrolled Mrs. Smith into this trial.

16 Anita Smith's enrollment process may  
17 represent a systematic approach to enrollment of  
18 questionable patients. Therefore, if the enrollment  
19 process is put into question, then the study  
20 findings that Biogen Idec has publicized widely in  
21 recent reports must also be put into question.

22 Anita Smith's death has caused close

1 examination in the literature. Her autopsy report  
2 was published in the New England Journal of  
3 Medicine in 2005, and the results of that autopsy  
4 report indicate that she did not have any  
5 histopathological evidence of MS. In fact, the  
6 report showed widely disseminated PML and evidence  
7 of possible vasculitis.

8           The enrollment MRI I obtained on court  
9 order was not available to the New England Journal  
10 of Medicine at the time that the report was made  
11 regarding her clinical history and ultimate demise.

12           The British Medical Journal and Lancet  
13 have recently published articles also questioning  
14 whether or not, in fact, Anita Smith had MS, and  
15 the possibility that this drug will be continued to  
16 be used in patients who may not be suitable  
17 candidates for its use given the possibility of  
18 mortality.

19           Why Anita Smith's case is so important to  
20 the panel today, the panel must question, as many  
21 other experts have, the serious implications of how  
22 and why Anita Smith was enrolled and possibly how

1 other patients were enrolled as well, especially  
2 since new clinical trials by Biogen Idec are  
3 anticipated and possible approval of Tysabri for  
4 clinical use is anticipated.

5 Thank you.

6 MS. CASANOVA: My name is Lisa Casanova.  
7 My trip here is not sponsored by anyone. I am  
8 speaking only for myself.

9 I was a participant in the Phase III and  
10 open-label trials of Tysabri for Crohn's disease,  
11 which I have had for 20 years, since I was 7 years  
12 old.

13 I know that this committee is not  
14 considering bringing back Tysabri for the treatment  
15 of Crohn's, but the benefits I got were so great,  
16 and I believe that this is so important, that I am  
17 here to ask you to bring this drug back on the  
18 market for the people it can help.

19 Before I went into the trial, I was facing  
20 a major surgery to remove part of my large  
21 intestine that has been damaged beyond repair by  
22 this disease. Tysabri allowed me to delay that

1 major surgery for almost three years. For a  
2 Crohn's patient, that is a long time.

3 It allowed me to live with less pain, it  
4 improved my quality of life. I went into the  
5 Tysabri trial to test an unknown drug with unknown  
6 risks, because I firmly believe that that is the  
7 only way we are going to see progress.

8 I thought the risks were worth it, and my  
9 heart goes out to the people who suffered as a  
10 result of their choice to participate, but I still  
11 believe those things. I am willing to take the  
12 risks and I can only imagine how much more willing  
13 these MS patients are who have such a terrible  
14 disease and so few choices.

15 I understand the place that they are in.  
16 When you live with life-long debilitating disease,  
17 all of your choices are tradeoffs. No one can tell  
18 you, you just need to do this one thing, and  
19 everything is going to be okay.

20 Right now I control my disease with drugs  
21 that put me at risk of lymphoma, of infections, of  
22 liver damage. My other options carry similar risks

1 with them.

2 For us, it is a series of tradeoffs  
3 between drugs, surgeries, between the quality of  
4 life that we want to have for ourselves, and the  
5 chances that we are willing to take to get that  
6 quality of life. That is the reality that we live  
7 with every single day of our lives, and it is not a  
8 reality that is ever going to be made better by  
9 having fewer options.

10 I know that this drug is not going to come  
11 back for Crohn's patients. When it comes to real  
12 therapeutic progress, our day hasn't come yet, but  
13 I am always hopeful that it will, and in the  
14 meantime, I believe that you need to do the right  
15 thing and bring this drug back to the market for  
16 the people it can help.

17 Thank you.

18 MS. CLARK: Thank you for listening to my  
19 personal experience with Tysabri. My name is  
20 Pamela Clark, and I have had MS for 10 years. I  
21 have progressed from relapsing-remitting to  
22 secondary progressive.

1           My mother and I traveled here from Phoenix  
2   and Salt Lake City respectively. We paid for our  
3   own ticket, and we are not sponsored by any  
4   organization.

5           It was important that my mom be here,  
6   because she has two daughters with multiple  
7   sclerosis, and she was the one who held my hand  
8   during my first Tysabri infusion. In the weeks  
9   after the infusion, she witnessed the improvement  
10   in my gait and my energy level. We were ecstatic  
11   and we were filled with hope.

12          You see, she fought her own battle with  
13   cancer 15 years ago, using then risky and then  
14   experimental drugs. Today, she is cancer-free and  
15   those experimental drugs are widely used by people  
16   with cancer every day. As a family, we understand  
17   the risks of using experimental drugs, but we also  
18   understand the risk of doing nothing.

19          The risk of doing nothing for me is too  
20   great. The risk of doing nothing, which for me  
21   means continuing to take ineffective drugs, is too  
22   high for me to ignore. I must fight for the right

1 to have the opportunity to live life to its  
2 fullest. I owe it to myself and I owe it to my  
3 family.

4 I attend a MS physical therapy group three  
5 days a week. It is comforting to be among people  
6 who have the same affliction, and they understand  
7 my struggles completely. It is not comforting,  
8 however, to watch my friend's health falter and  
9 fail. It is not comforting, however, to watch my  
10 friend, who walked in on a cane last year, roll in  
11 in a wheelchair.

12 This disease and its symptoms are  
13 progressive and they will not wait for anyone's  
14 approval. The drug they take do not stop or even  
15 slow the progression of MS. Finding an effective  
16 treatment seemed hopeless. That was I felt  
17 hopeless until I found Tysabri last January or  
18 January of 2005.

19 In January of 2005, I had two infusions of  
20 Tysabri and I got better, not miraculous jump up  
21 and run a race better, but I did walk to the duck  
22 pond with my two, five-year-old boys. I did stand

1 up and cook dinner, stand up long enough to cook  
2 dinner, and I did smile more often. That is what  
3 hope does. That is what Tysabri did for me.

4 On the issue of risk management that you  
5 have been talking about this morning with Tysabri,  
6 I received monthly Solu-Medrol infusions at the  
7 infusion clinic in my neurologist's office, and  
8 there, Julie and Martha, who I know from being  
9 there monthly, every month, they sit down with me,  
10 and they have a questionnaire already, and they  
11 say, "What are your symptoms like? What have  
12 changed?"

13 This new reporting mechanism will be no  
14 different for them, and I know that they will  
15 gladly do it.

16 The cost of getting here is high for me,  
17 both the cost of our travel expenses and the cost  
18 to my health. The stress--.

19 DR. HUGHES: Thank you for allowing me to  
20 speak. My name is Chris Hughes. I am a  
21 board-certified neurologist, and I have been in  
22 private practice for 12 years.

1           Within the past year, I have signed  
2   consulting agreements with Biogen, Berlex, Serono,  
3   and Teva, but I am here today at my own expense to  
4   state that in my opinion, the current state of  
5   therapeutics for multiple sclerosis is remarkable,  
6   and the future with new drugs in development is  
7   even more encouraging.

8           Through the 1990s, beta-interferon and  
9   Copaxone were FDA-approved for the treatment of MS.  
10   We now have over 10 years of experience with both  
11   of these agents, and numerous studies demonstrating  
12   their safety and efficacy in slowing the  
13   progression of the disease.

14           We are just now learning from new studies  
15   that early initiation of these established  
16   therapies further improves their effectiveness.  
17   Today, with the use of these medications, the  
18   severely affected multiple sclerosis patient is  
19   still part of our clinic, but make up a smaller  
20   percentage than they did in the past.

21           Yes, interferons and Copaxone have  
22   revolutionized the state of our MS patients for the

1 better. Further, we hope that combining these two  
2 agents proves synergistic and studies addressing  
3 this subject are planned. Further, the higher dose  
4 interferons and study of this are also underway.

5 For interferons and Copaxone, in my  
6 opinion, the best is yet to come, and for those  
7 patients with aggressive disease, we have another  
8 FDA-approved drug, obviously Novantrone, which is a  
9 highly effective agent.

10 Regarding Tysabri, in the initial New  
11 England Journal report, investigators identified 4  
12 out of 142 patients that had serious side effects  
13 related to Tysabri, one of which was anaphylactoid,  
14 a state that most community neurologists are not  
15 well equipped to treat in an office setting.

16 Since its withdrawal, I have attended many  
17 scientific meetings in which the issue of Tysabri  
18 and PML has been discussed. Many of us fear that  
19 with the reduced immune cell migration effect of  
20 this drug, longer exposures to Tysabri could  
21 exponentially increase the risk of opportunistic  
22 infection or latent virus reactivation, and I have

1    seen no data to reassure that concern.

2                So, in summary, beta-interferons,  
3    Copaxone, and Novantrone are highly effective  
4    agents. High-dose interferons and combined therapy  
5    hold additional promise for new agents, and also we  
6    have new medications in development.

7                In this context, I would argue that there  
8    is no crisis in MS therapeutics, and therefore no  
9    need to rush back to the market a drug that has  
10   serious proven hazards given the lack of safety  
11   data in longer term use.

12              I would urge further study of Tysabri and  
13   its relationship to PML. Only with longer term  
14   safety data can neurologists feel comfortable using  
15   this drug in the future.

16              MS. LADD: Mr. Chairman and members of the  
17   Advisory Committee, thank you for the opportunity  
18   to address the pending biologics license  
19   application for Tysabri. My name is Virginia Ladd,  
20   and I speak as President and Executive Director of  
21   AARDA, the American Autoimmune Related Diseases  
22   Association.

1           AARDA maintains strict and transparent  
2     guidelines for commercial contributions. Neither I  
3     nor AARDA have received financial relationship or  
4     funding from the sponsors of Tysabri, Biogen Idec,  
5     or Elan Pharmaceuticals, nor does AARDA endorse any  
6     product or services.

7           AARDA is the only national voluntary  
8     health agency advocating for all of the more than  
9     22 million Americans afflicted with 100 autoimmune  
10    diseases. We do this through education and  
11    research and patient services.

12           On behalf of AARDA and its members, I  
13    thank this committee for its critically important  
14    work. Tysabri is an important new therapy for  
15    multiple sclerosis. FDA's decision on this  
16    application will directly affect hundreds of  
17    thousands of MS patients nationwide and have  
18    important implications for patients with other  
19    autoimmune diseases.

20           That is why we are pleased that FDA  
21    emphasized last year that it places particular  
22    importance upon patients' views of Tysabri.

1           AARDA urges the committee to keep the  
2   question of patient choice uppermost in mind as it  
3   proceeds with its important work. The potential  
4   reintroduction of Tysabri to market with  
5   appropriate safeguards would enable fully informed  
6   patients to make reasoned decisions about their own  
7   health care.

8           FDA made this point forcefully when the  
9   Agency explained its decision to permit the market  
10   reintroduction of Lotronex in 2002, quote,  
11   "Physicians are essential in determining the  
12   benefits and managing the risks of an individual  
13   patient for whom the drug is prescribed.  
14   Ultimately, the patient, once informed, is the  
15   definitive decisionmaker concerning the  
16   benefit-risk balance."

17           Our members have made clear that decisions  
18   like Tysabri should only be made when the  
19   decisionmakers understand fully that patients with  
20   chronic diseases may view the balance of risk and  
21   benefits differently from physicians, regulators,  
22   and other stakeholders, not simply because they are

1 not informed or because they cannot fully  
2 understand the issue at hand, for a patient with a  
3 chronic illness, the potential value of a therapy  
4 that allows him or her to leave their wheelchair  
5 behind or go back to work may make that patient  
6 willing to take risks that would be unacceptable to  
7 someone else.

8 Just as the generalization cannot be made  
9 that no one drug will be effective for everyone,  
10 neither can it be said that a drug will have the  
11 same safety issues in all treated individuals.  
12 With the right information and advice of their  
13 caregivers, it would be a grievous mistake to  
14 underestimate the capacity of MS patients to  
15 recognize, understand, assess, and assume the risk  
16 or the potential benefits of a product like  
17 Tysabri.

18 This is not a novel point, but it bears  
19 emphasis in this proceedings. I have submitted for  
20 the record, AARDA's position paper, "A greater Need  
21 for Patient Voice and Choice," that addresses the  
22 vital importance of patients participation in the

1 clinical, as well as the regulatory, decisions that  
2 determine the therapeutic choices available that  
3 determine our health and our quality of life.

4 AARDA believes that Tysabri's  
5 effectiveness is well established and it is a very  
6 important as a first in class novel therapy for MS.  
7 We believe that Tysabri's market experience,  
8 clinical investigation, and reports from patients  
9 and providers demonstrate its important clinical  
10 benefits.

11 Effective new therapies are few and far  
12 between for autoimmune diseases generally and  
13 specifically with MS. Therapeutic regimes for  
14 autoimmune diseases are clinical juggling acts of  
15 multiple medications that must constantly be fine  
16 tuned to avoid and manage relapse and flare-ups.

17 The availability of novel, new therapies  
18 is critically important to our members.

19 Finally, AARDA recognizes that FDA has  
20 been under intense public and congressional  
21 scrutiny in relation to post-market safety of drugs  
22 and biologic products, but we urge the committee

1 and FDA to act strictly on science, clinical  
2 evidence, and availability of appropriate labeling,  
3 risk management controls, and post-market studies  
4 in deciding whether Tysabri should be returned to  
5 the market.

6 MS. CANAVAN: Hello. My name is Emily  
7 Canavan. I have no financial ties with any  
8 pharmaceutical company, and no one contacted me to  
9 come here today.

10 I am 27 years old and I was diagnosed with  
11 MS in 2003. My mother was diagnosed in 1999. I  
12 was 24 years old when my life as I knew it ended.  
13 It was a life where I was a hiker, an athlete, a  
14 teacher, and an adventure traveler.

15 My health has declined rapidly. For  
16 someone like me, time is precious. I have never  
17 experienced any real period of remission and no  
18 medications have stopped or slowed my MS from  
19 progressing.

20 I cannot convey to you how difficult it is  
21 to watch my friends travel, work, and excel while I  
22 am held hostage by multiple sclerosis. In 2002, I

1 received a Master's Degree and teaching students  
2 with emotional and behavioral disabilities.

3 During the 2001-2002 school year, I taught  
4 every day, had class four nights a week, and at 23,  
5 I had found something I loved and I was good at.  
6 After graduation, I began teaching fifth grade.  
7 Four months later, I had to go out on disability.  
8 By then I had daily headaches so bad that I could  
9 not get out of bed.

10 My mother had been diagnosed with MS four  
11 years before, but I kept telling myself I am just  
12 stressed out, this is not MS. I clung to this  
13 statement as hard as I could, but in the next six  
14 months I developed painful muscle cramps, constant  
15 urinary problems, tingling, cognitive problems, and  
16 my mobility became very limited.

17 Some days it's two steps, and some days  
18 it's two blocks. These new symptoms and an  
19 ever-growing number of lesions on my brain finally  
20 confirmed the diagnosis of MS. To add insult to  
21 injury, last year I was diagnosed with ulcerative  
22 colitis. Colitis and Crohn's disease both involve

1 inflammation in the intestines, and Tysabri during  
2 trials gave many Crohn's patients an improved  
3 quality of life.

4 Less than a year after leaving my job, I  
5 had to move out of the city and closer to my  
6 family, because I need help so often. My headaches  
7 continue to be debilitating and other symptoms  
8 persist. I have had to adjust to using an electric  
9 scooter. I have to consider how to transport it,  
10 investigate each location's accessibility, and deal  
11 with the reality that when you are in your 20's and  
12 on a scooter, people are going to stare.

13 I have exhausted most MS treatments  
14 already. AVCRs, IVIG, methotrexate, Solu-Medrol,  
15 LDN. I am not currently on any MS treatment drug.  
16 I had one dose of Tysabri the week it was taken off  
17 the market. I am reluctant to take strong  
18 chemotherapy drugs because of the risk of  
19 infertility, but that's the point. Every patient  
20 has to weigh the benefits and risks of every  
21 medication.

22 I haven't been willing to risk

1   infertility, but if nothing else helps, that risk  
2   will become worth it to me. All medications have  
3   risks, even over-the-counter medications can be  
4   deadly if taken inappropriately or by people with  
5   certain conditions.

6               I will be extremely disappointed if  
7   Tysabri doesn't help me, however, I will be glad I  
8   came to this hearing because it will help so many  
9   people whose lives have been turned upsidedown by  
10   MS. It may help me, it may help my mother.

11              DR. STUART: My name is Bill Stuart. I am  
12   the Medical Director at the MS Center of Atlanta,  
13   which is a foundation-run public charity center.  
14   We see over 100 patients with MS a day, five days a  
15   week.

16              I have been in neurology practice for 36  
17   years. The last 16 years I have done almost  
18   exclusively MS, so I have an intimacy with this  
19   disease that I would like to share with you.

20              That is, that it is a disease. When my  
21   center was at the Shepherd Center, which is a large  
22   spinal cord treatment center in Atlanta, one of the

1 things that became apparent to me is that spinal  
2 cord injury patients and MS patients with  
3 comparable disabilities function differently.

4 The MS patients never took advantage of  
5 the therapeutic recreational facilities, whereas,  
6 the other group did. They had vigor, they had  
7 interest, and it dawned on me that MS is more than  
8 just a disability, it is also an illness, and it is  
9 the illness part we don't measure very well.

10 In my observations through the years, I  
11 think that the reasons people leave active life  
12 because of MS are largely due to cognitive change,  
13 excessive fatigue, pain, sleep disorders, bladder  
14 and bowel issues, and sexual dysfunction.

15 The second point I would like to make has  
16 to do with how we would enter a person into the  
17 study, relapsing-remitting has been proposed. I  
18 would suggest that that will create a number of  
19 problems. First of all, recordkeeping will be  
20 fudged. Every patient will have  
21 relapsing-remitting disease if the doctor treating  
22 the patient desires to try Tysabri.

1 I would suggest that you consider a term  
2 called "worsening MS," and work at trying to define  
3 what worsening MS is.

4 The third issue is a socioeconomic issue.  
5 In our center, the actual day-to-day medical care  
6 of the MS patient is in the red. If we add onerous  
7 risk management type efforts to this in the  
8 opportunity to give Tysabri, we won't be able to  
9 use the drug, it will be impossible, because it  
10 will drive our losses even higher. The losses now  
11 are offset by contributions and other collateral  
12 revenue streams.

13 I think that the Biogen plan for  
14 monitoring patients was quite a reasonable plan,  
15 and I would favor that you endorse that.

16 Finally, there is a crisis in MS care, and  
17 it has to do with compliance. We currently have  
18 compliance rates that are terrible. We have as  
19 many patients going off of the medicines that we  
20 have today as are going on them, so that we are a  
21 steady state in trying to treat these patients, and  
22 that steady state is well below where we should be.

1 Thank you very much.

2 MS. COOKSEY: My name is Christy Cooksey.

3 I have traveled here from Coos Bay, Oregon, to  
4 represent my mother, Janet Russell, in Klamath  
5 Falls, Oregon, who is too disabled to make the trip  
6 due to her MS disability.

7 I would like to disclose that I have no  
8 financial interest in either Biogen or Elan, nor  
9 have I received any financial support from either  
10 company.

11 My mom has written a letter to this  
12 committee, which you all have in your packets, and  
13 I hope that you will read it. You will hear her  
14 words, but I would like to describe to you what it  
15 is like to watch your mom be destroyed by this  
16 horrible disease.

17 My mom is my hero. She is one of the  
18 strongest people that I know. She jokes about her  
19 disability saying things like "I'm going to be the  
20 first disabled stunt woman," referring to her  
21 constant falling.

22 My mom is my best friend and I have been

1 devastated having to watch her quality of life  
2 diminish so rapidly. Her inability to travel has  
3 impacted our entire family. I currently live four  
4 and a half hours away from my mother. For my mom  
5 to travel to visit me and my two children, it takes  
6 her two days as she has to stop halfway to rest.

7 If she were to attempt the trip in one  
8 day, she would be so fatigued the next day, all she  
9 would do is to sleep to recover.

10 I have witnessed many of my mom's symptoms  
11 and also her sometimes horrible reactions to at  
12 least three different, quote "treatments" she has  
13 been on. These include flu-like symptoms,  
14 uncontrollable shaking, injection site reactions,  
15 and possible bone loss.

16 At one point, she experienced a total loss  
17 of control of her legs and an actual increase in  
18 her relapses while on these treatments. Tysabri  
19 has been her miracle, and she needed it back a year  
20 ago.

21 With only one infusion, her muscle spasms  
22 all but disappeared, allowing her to walk without

1 her walker, and without falling. She was less  
2 fatigued, her cognitive abilities improved, her  
3 speech was less slurred, and her beautiful singing  
4 voice, which she lost in 1999 due to her MS, was  
5 finally coming back.

6 On a follow-up visit with her neurologist,  
7 he saw her improvements and stated, quote, "If you  
8 think the first infusion helped, just wait until  
9 you get the second or third." She never got the  
10 chance to get her second.

11 The MS community has a tremendous unmet  
12 medical need for effective treatments for this  
13 horrible disease. Every day my mom suffers the risk  
14 and the reality of her disability progressing.  
15 This is a much greater risk than Tysabri if it was  
16 used in compliance with the risk management plan.

17 My mother is more than willing to  
18 participate in any form of risk management program  
19 approved by this committee. My mom and our family,  
20 along with her neurologist, want to have a choice  
21 in which treatment is most appropriate for her to  
22 slow, stop, or possibly reverse the progression of

1 her disease.

2 MS. LYONS: I don't own stock in Elan, I  
3 don't own stock in Biogen Idec. I occasionally  
4 speak for Biogen Idec as part of a voluntary group.

5 I am K.T. Lyons, and I am an MS survivor.  
6 I am one of those who was first diagnosed by a  
7 general practitioner, just kind of had an idea that  
8 I might have MS from my on and off symptoms, and  
9 his idea was since I have had these on and off  
10 symptoms for more than eight years, why didn't we  
11 just watch it.

12 So, indeed, that is what we did. I  
13 continued my job in a Fortune 500 company, and I  
14 continued running two miles a day until that one  
15 day in 1977 when I woke up, blind in one eye,  
16 completely unable to speak, and having great  
17 difficulty in breathing.

18 I was hospitalized and finally a  
19 neurologist was called in, and they came in with  
20 the permanent diagnosis that I did have MS. So, I  
21 had steroids for my eye and some physical therapy,  
22 and I was put on an interferon and sent home.

1 I am one of those who had sickness and  
2 depression on the interferon, but nonetheless, I  
3 continued with my life. My disease continued to  
4 worsen, so they tried IVIG, they tried another  
5 interferon, and then finally, they tried  
6 Novantrone. None of this worked, and I continued  
7 to have relapses more often and more often.

8 Finally, just to try to improve the other  
9 part of my wellness, I began an involvement with  
10 the Bureau of Vocational Rehabilitation, and found  
11 out there might be a way that I would go back to  
12 work.

13 They enabled me to start my own business,  
14 which I did start, and got on my way to at least  
15 beginning to feel better. Then, in 2005, the level  
16 playing field that I thought I had gotten onto  
17 changed again.

18 I am in severe pain and have difficulty  
19 talking all the time from a little known symptom of  
20 MS called trigeminal neuralgia, and I take a drug  
21 for that, that is an anti-seizure drug, and the  
22 drug had built up in my system way too much, and I

1    went unconscious.

2                   I remained unconscious in the hospital for  
3    more than nine hours, because the combination of my  
4    MS lesion and the tegretol had placed me in such a  
5    dangerous position.  When the hospitalist came in  
6    and when the neurologist came in--.

7                   MS. LAWSON:  I would like to disclose that  
8    I have received remuneration in the past from  
9    Biogen Idec.  My expenses associated with this open  
10   public hearing are being paid through personal and  
11   private funds.

12                  Thank you very much for this opportunity  
13   to speak with all of you.  My name is Sonda Lawson.  
14   I am a licensed counselor and director of MS  
15   Clinical Research and Services at the Michigan  
16   Institute for Neurological Disorders MS Center.

17                  MIND has a comprehensive MS care facility  
18   servicing over 2,000 MS patients.  I am speaking to  
19   you today from both a personal and a professional  
20   perspective.

21                  I was diagnosed with MS 10 years ago, but  
22   have really been living with the disease for over

1 15 years now. Although outwardly no one would know  
2 that I have MS, there isn't a day that goes by that  
3 I don't have some reminder whether it's residual  
4 visual deficit from multiple bouts of optic  
5 neuritis, bladder issues, numbness, weakness,  
6 clumsiness, or seeing how my MRI continues to  
7 worsen.

8           Although I try not to live my life  
9 wondering what could happen to me, the reality is  
10 that in the back of my mind, I do fear that today  
11 or tomorrow the disease could manifest into  
12 something very significant.

13           It is very real because the threat is  
14 present and looming on a daily basis. I watch this  
15 disease slowly or aggressively destroy people's  
16 lives.

17           When I was diagnosed, the images that were  
18 portrayed were those of essentially a wheelchair  
19 sentence, and Dr. Kevorkian was helping MS patients  
20 commit suicide because they couldn't bear to live  
21 as essentially vegetables.

22           I distinctly remember all the literature

1 indicated that a cure was 5 to 10 years away.

2 Well, here we are now, 10 years later, and we are  
3 not even close to a cure.

4 I started working in MS Research in 1999  
5 in an effort to help in any way that I could find  
6 more options for our patients in the fight to end  
7 the devastating effects of this illness.

8 Over the last four-plus years, I have had  
9 the unique opportunity to serve as the research  
10 coordinator in four different Tysabri clinical  
11 trials with a cumulative total of 56 patients.

12 In addition, I personally received four  
13 doses of Tysabri, and after taking injections for  
14 over 10 years now felt so liberated to not undergo  
15 the myriad of side effects and dosing regimen  
16 involved with injections.

17 For the first time, I felt more in control  
18 of my illness, and so the impact it had on my  
19 emotional and physical wellbeing was profound. My  
20 experience is not unique. Virtually, every one of  
21 our patients is eager to resume taking Tysabri.

22 Although Tysabri doesn't represent the

1 answer, it represents better preservation until we  
2 can find the answer. Unfortunately, no matter how  
3 the data is tweaked, the current approved  
4 medications used to treat MS today are only about  
5 30 percent effective.

6 Tysabri has been shown to be far more  
7 efficacious than any of the current options. Yes,  
8 there is a risk, but if you look at the biologic  
9 pipeline, are we ever really going to take away the  
10 element of risk.

11 Furthermore, having MS is our biggest  
12 risk. I understand we live in a litigious society.  
13 The FDA, pharmaceutical companies, and physicians  
14 are appropriately concerned about patients overall  
15 safety.

16 As a research coordinator, I have reviewed  
17 the new safety measures and consent documentation  
18 required from each candidate that will receive  
19 Tysabri in the reinfusion trial.

20 Furthermore, I can speak at least on  
21 behalf of our facility. There will be a treatment  
22 algorithm that we will follow in order to minimize  
23

1 and manage the risk to the extent that we can.

2 Thus, I am confident those that wish to  
3 receive this therapy will be well informed of the  
4 potential risks, and as their healthcare provider,  
5 we will be hypervigilant when it comes to  
6 monitoring our patients and managing their care.

7 In conclusion, I sit before all of you  
8 today as a clinician and a patient of MS. I am in  
9 the unique position of intimately knowing the risks  
10 and benefits of this disease and its medications.  
11 We live in a world where many neurologists view the  
12 treatment of this disease as one that should be  
13 without risk because MS is not terminal, but rather  
14 a manageable disability.

15 So, I ask you how can any physician,  
16 pharmaceutical company, or governmental  
17 organization determine my/our disability as  
18 acceptable or manageable? We, as patients, should  
19 be able to decide.

20 My final note that I leave with you today  
21 is an analogy I often use in regards to MS. Any of  
22 us can get hit by a bus. The difference is those

1 of us affected with MS see the bus coming. The bus  
2 for us represents disability, and it's imperative  
3 that we have as many choices as possible to slow  
4 the bus down.

5 I truly believe that Tysabri represents a  
6 better alternative to slowing the bus down.  
7 Tysabri may not be for everyone, but it is another  
8 option to add to our armamentarium.

9 Thank you.

10 MS. CROOKS: Good afternoon. My name is  
11 Barbara Crooks and I am here to defend Tysabri, and  
12 I have not been paid by anyone to be here.

13 Life is all about tradeoffs. I was  
14 diagnosed with MS eight years ago, and at that time  
15 I was a very active 40-year-old, married, mother of  
16 two, who had a very fulfilling job as a registered  
17 MRI technologist, working in the neuro field for  
18 over 25 years.

19 I have a wonderful family who all had  
20 their input as to what I should talk to you about  
21 today. My father wanted you to know that I was  
22 district champion in hurdles in high school. I ran

1 cross country in college, survived a 50-mile bike  
2 race, did hours of aerobics, weight training, and  
3 probably walked 473,000 miles in my neighborhood.

4 I played basketball with my son and rode  
5 horses with my daughter, and then the MS monster  
6 hit. I have traded my active lifestyle for a life  
7 of isolation in my home as you can see by the way I  
8 walk.

9 Throughout the years, I have struggled  
10 just to keep my legs under me going from one  
11 FDA-approved drug to another. I have been on  
12 hundreds of steroids - Avonex, then, I doubled  
13 Avonex, which after relapsing again, I traded  
14 double-dose Avonex with single-dose Avonex and  
15 Copaxone, only to relapse again.

16 I then traded that combination for Avonex  
17 with Mitoxantrone, and most recently I had to trade  
18 Tysabri for Imuran. All of these drugs with their  
19 side effects of flu symptoms, nausea, and weakness  
20 only helped temporarily.

21 This, combined with my underlying MS  
22 symptoms of back pain, hip pain, right foot drop,

1 balance, and vision issues, and fatigue contributed  
2 to the decline of my wonderful life and the loss of  
3 my job. My patients walked better than I did.

4 Then, there was Tysabri, absolutely the  
5 easiest and the only positive treatment that I have  
6 ever taken. With the one-hour injection time and  
7 only slight nausea, I was able to return home  
8 feeling great, slept great, woke the next day with  
9 no pain.

10 This shocking discovery led to improved  
11 walking and mobility for the first time in over a  
12 year. Had I been able to continue the Tysabri  
13 treatment, I believe that I would have been  
14 protected from further attacks and given the  
15 improved quality of life that I strived for.

16 After my third dose, Tysabri was pulled  
17 from the market. While I understood the decision,  
18 I told my husband, Dave, that I would sign a waiver  
19 to continue the drug even with the risk of PML.  
20 Naturally, my comment upset him, fearing of losing  
21 his wife of 24 years.

22 As a Christian, I am not afraid of dying,

1 but I am afraid of living as a burden to those I  
2 love. Soon afterwards while running a couple  
3 errands, he was struck by my difficulty in  
4 performing simple, everyday tasks, which are taken  
5 for granted by the average person.

6 This realization led him to understand why  
7 I would risk taking this drug in order to regain  
8 the basic quality of life that I crave. The  
9 technicalities of how Tysabri binds with the  
10 potentially damaging immune cells from the  
11 bloodstream and interferes with crossing the  
12 blood-brain barrier can be left to all the experts  
13 in that area.

14 I am coming to you humbly, as a wife, a  
15 mother, a daughter, sister, sister-in-law, and a  
16 friend--.

17 MR. LORE: My name is Steve Lore and I  
18 have no financial interest in whatever outcome  
19 comes about because of today's hearing.

20 I was diagnosed with MS in 2001, not a  
21 great year for the country, and not a great year  
22 for me. But after diagnosis, I went through a

1 whole regimen of treatments I did the ABCs, Rebif,  
2 Avonex, Copaxone, and all without really much  
3 improvement in the disease.

4 So, my doctor then put me on Solu-Medrol,  
5 and then we tried different things, IVIG. We have  
6 finally, most recently, done Novantrone and  
7 Retuxan. Now, those are drugs that have potential  
8 side effects that are not very good, but they are  
9 just potential side effects, just like with  
10 Tysabri. PML is a potential side effect, and I  
11 choose to take that risk of that side effect,  
12 because I had one dose of Tysabri, and with that  
13 one dose, I felt like my life had been given back  
14 to me.

15 I felt so much better after just one dose,  
16 and it was pulled before I got the second dose.  
17 Who knows what would have happened had I had two or  
18 three doses. Hopefully, I will get a chance to do  
19 that before very long.

20 It all comes down to a risk versus  
21 benefits, and I think the benefit of having it out  
22 there for people to have the choice to take it,

1 because the choices are very limited in scope.  
2 There are not that many choices out there, so this  
3 was a huge advance for the treatment of a very  
4 debilitating disease. It is like looking down a  
5 well. If you fall into the well, you are not going  
6 to get out of it very easily, and MS is like that.  
7 It is not a disease that has many ups.

8           There are not many high points in the  
9 disease of multiple sclerosis. It's all of  
10 aggression that gets worse and worse and worse,  
11 and, you know, hope is a great thing, and I felt  
12 that with Tysabri, there was hope.

13           Thank you.

14           MS. BLOOM: My name is Cheryl Bloom and I  
15 live in Idaho, and I am disclosing that I own 300  
16 shares of Elan stock, and I am here on my own.

17           "But you look so good." That is what  
18 people tell me all the time, but I don't feel good.  
19 On a daily basis, I fight fatigue, dizziness,  
20 spasticity, permanent numbness, and pain. I was  
21 once an aerobatic pilot.

22           Since my diagnosis of MS in March of 2001,

1 at the age of 48, my life altered drastically. I  
2 am here today to talk to you about how my life  
3 changed for a few short months when I had the  
4 choice to have Tysabri infusions in early 2005.

5 I have a very active case of  
6 relapsing-remitting MS in which I have  
7 exacerbations every three months. None of the  
8 current disease-modifying drugs nor therapies have  
9 done anything to slow down this exacerbation rate.

10 I have been on Betaseron, Betaseron  
11 combined with methotrexate, and Copaxone. To  
12 control these exacerbations, I must have  
13 I.V.-administered Solu-Medrol for a minimum of  
14 three days. The long-term adverse effects of  
15 Solu-Medrol are not reversible.

16 If you add up all of the three-day  
17 Solu-Medrol infusions I have had over the past five  
18 years, that is a lot of steroid damage to my body.  
19 The short-term side effects of infused Solu-Medrol  
20 are life altering for me.

21 I cannot work, nor perform such simple  
22 daily tasks as cooking dinner for my husband due to

1 debilitating fatigue. It takes almost two weeks  
2 for my life to get back to my normal after an  
3 exacerbation and I.V. Solu-Medrol.

4 When my neurologist recommended that I try  
5 Tysabri, I was ready to try anything. The first  
6 two infusions in January and February 2005 went  
7 very well with no side effects. Amazingly, I felt  
8 like a normal person again, like a person without  
9 MS.

10 I was scheduled for the third infusion on  
11 March 3rd, 2005. Unfortunately, I was unable to  
12 have this infusion because Tysabri was pulled from  
13 the market, but the effects of the drug were enough  
14 that I had no exacerbations for five months.

15 Tysabri is the most effective  
16 disease-modifying treatment currently known for  
17 relapsing-remitting MS, and people with MS should  
18 have the choice of Tysabri available to us as long  
19 as we have all the information known about the  
20 potential risks and benefits.

21 Every drug carries risks of side effects,  
22 even Zantac, a drug to which I had an acute

1 anaphylactic reaction. People with MS have a right  
2 to decide what risks are acceptable to us for an  
3 effective treatment as long as information about  
4 the risks is not concealed.

5 I assure you I will adhere to every  
6 element of any risk management plan implemented.  
7 Please do not make us wait any longer for Tysabri.

8 MR. BARRON: Hi. I am Mike Barron. I am  
9 48 years old. I proudly served my country as a  
10 nuclear engine room supervisor aboard the  
11 nuclear-guided missile cruiser USS Texas, CGN39.

12 I was honorably discharged from the U.S.  
13 Navy and began a civilian career in the nuclear  
14 electrical generation industry. In December of  
15 1985, I developed severe optic neuritis of my right  
16 eye, but continued to qualify until I received my  
17 nuclear reactor operator's license for Pala Verde  
18 nuclear generating stations Units 1, 2, and 3.

19 I safely and effectively operated all 13  
20 nuclear plants until I suffered another major  
21 exacerbation and was officially diagnosed with  
22 multiple sclerosis on February 28th, 1995.

1           In mid-1995, I was found medically  
2   disabled by MS and placed on Social Security and  
3   private pension. My specialist prescribed me  
4   interferons for over nine years. During that time,  
5   I found out about Antegren as a MS drug showing  
6   great promise.

7           Because of my belief in that new hope for  
8   my MS, I took a small position in Elan stock in  
9   2002. In late 2003, I began having severe  
10   abdominal lower extremity spasticity attacks as  
11   very painful charley horses.

12          After studying the drug with the help of  
13   my doctor, I began preparation for getting my first  
14   dose. In October of 2004, I quit Betaseron without  
15   telling my doctor because I felt it was making me  
16   sicker, and it wouldn't interfere with the Tysabri.

17          On January 5th, I received my first  
18   Tysabri infusion. I received my second infusion on  
19   February 4th. I started feeling so good about  
20   myself, I started doing more things around our  
21   home. I started taking walks with my wife again.  
22   I started feeling so good about myself, I couldn't

1 feel like I had MS anymore basically. It was going  
2 away.

3 Not only was I feeling better, I was  
4 sleeping better at night. then, on February 28th,  
5 2005, they took my Tysabri away. I decided to get  
6 actively involved to find out why my Tysabri was  
7 taken away.

8 I even volunteered and became a non-paid  
9 Biogen MS patient advocate, and after contacting  
10 the FDA and figuring out what needed to be done to  
11 improve the patient feedback to the FDA, I quit my  
12 Biogen patient advocacy, which leads me to why I am  
13 here today.

14 I want to let you know that I am fully  
15 capable and willing, with the help of my chosen  
16 professional, to engage the possible risk of 1 in  
17 1,000 in order to achieve a much higher quality of  
18 life for me and my wife.

19 I truly believe that Tysabri is the cure  
20 for the active component of my dynamic MS. I would  
21 really like to become productive again and give up  
22 my 24/7, 365-day job as an MS patient and get a

1 working man's job to pay taxes again.

2 Thank you.

3 MR. RICHERT: Thank you for the  
4 opportunity to speak at this hearing. My name is  
5 Dr. John Richert and I serve as the Vice President  
6 for Research and Clinical Programs at the National  
7 Multiple Sclerosis Society.

8 Prior to assuming this position one year  
9 ago, I was on the faculty at Georgetown University  
10 Medical Center, where I served as an investigator  
11 in the Sentinel trial of Avonex plus Tysabri. I  
12 currently serve on the Data and Safety Monitoring  
13 Boards for the Phase III trials of Novartis' FTY720  
14 and Acorda's Fampridine.

15 The mission of the Society is to end the  
16 devastating effects of multiple sclerosis. It is  
17 essential that people with MS have more choices for  
18 safe and effective treatments. We are grateful to  
19 the FDA for granting expedited review of this  
20 application.

21 Determining the relative risks and  
22 benefits for Tysabri is a complicated matter. Data

1 are being considered by the Advisory Panel that  
2 have not generally been in the public domain.  
3 There are also issues of risk for which there are  
4 no answers at this time.

5 The National MS Society has pursued all  
6 possible avenues to assure that the FDA brings  
7 together the expertise required to evaluate all of  
8 the data and to come to the best possible decision.

9 In this effort, we submitted a recommended  
10 list of potential panelists who, in our opinion,  
11 bring to the table a comprehensive and balanced  
12 understanding of the issues associated with the  
13 return of Tysabri to the market. We also provided  
14 recommendations on clinical and scientific experts,  
15 as well as people with MS, to speak at this open  
16 public hearing.

17 In order to assure that the FDA heard from  
18 every interested individual, we dedicated a  
19 month-long front-page link from our website to the  
20 FDA comment page. We also provided information on  
21 submitting testimony and participating in the  
22 hearings in person.

1           In December 2005, we commissioned an  
2   online survey of a random sample of over 800 people  
3   with MS, with particular emphasis on determining  
4   the amount of risk that they would be willing to  
5   accept and still take this drug.

6           The study was coordinated by International  
7   Communications Research with Harris Interactive  
8   Online and has a margin of error of plus or minus  
9   3.4 percent.

10          We have made the results of this survey  
11   available to the FDA. Of those who had heard of  
12   Tysabri, approximately 25 percent had a positive  
13   impression of the drug, 25 percent had a negative  
14   impression, and approximately 33 percent expressed  
15   a neutral opinion, wishing to have more information  
16   before making up their minds.

17          Twenty-six respondents had received  
18   Tysabri during its period of availability. Of  
19   these, approximately 76 percent wished to receive  
20   it again, 12 percent did not wish to receive it  
21   again, and 12 percent were undecided.

22          Among all survey respondents,

1 approximately one-third wished to have Tysabri  
2 available and half wished to have more information  
3 before making a decision.

4 In this survey, questions about acceptable  
5 degrees of risk were phrased in a manner such as:  
6 Would you wish to take this drug if the risk of  
7 dying from PML within 3 years is one in a thousand,  
8 or it's 1 percent, or 10 percent, and so on, right  
9 up to a 100 percent risk of dying from PML.

10 The responses were spread relatively  
11 evenly throughout the range, without a cutoff at  
12 any particular degree of risk.

13 We have been extremely fortunate that the  
14 approved disease modifying agents for MS have been  
15 extraordinarily safe. Similar degrees of safety  
16 are not seen among the medications available for  
17 treatment of most other autoimmune diseases.

18 Medications approved by the FDA for use in  
19 the treatment of rheumatoid arthritis, Crohn's  
20 disease, systemic lupus erythematosus, psoriasis,  
21 and ulcerative colitis, include those with degrees  
22 of known risk that include fatalities. These

1 medications include Enbrel, Humira, Kineret,  
2 Remicade, methotrexate, azathioprine, and Celebrex.

3 Patients suffering from these autoimmune  
4 diseases, along with their physicians, are learning  
5 to weigh the potential risks and benefits when  
6 making their treatment decisions. It is likely  
7 that our frame of reference for MS drugs will need  
8 to change to be more in line with the toxicity  
9 risks that are recognized in the treatment of other  
10 autoimmune diseases. The risks of the medications  
11 will need to be weighed against the risk of doing  
12 nothing.

13 If, after the safety review is complete,  
14 the FDA recommends Tysabri's return to the market,  
15 we will applaud the addition of this treatment to  
16 our arsenal.

17 If the FDA does not approve Tysabri's  
18 return to the market, or if it does so with  
19 significant restrictions, we will work tirelessly  
20 to find ways to satisfy the safety concerns so that  
21 more effective treatments can be readily available  
22 for the benefit of people with MS.

1 Thank you.

2 DR. KIEBURTZ: We have videos now.

3 MS. ROBERTS: Good afternoon, ladies and  
4 gentlemen. Thank you for allowing my videotaped  
5 testimony today. I had planned on being there in  
6 person, however, due to a recent exacerbation of my  
7 MS symptoms, I am no longer able to travel, and for  
8 the same reason, please excuse my slurred speech.

9 My name is Lauren Roberts. I am 51 and I  
10 live in California. I have been living with MS for  
11 30 years. As a long-time MS patient, I can tell  
12 you that there is a tremendous unmet medical need  
13 when it comes to MS therapies, because what is  
14 available to us today is ineffective for a large  
15 population of people with MS like me.

16 My MS started out 30 years ago being  
17 fairly mild with only numb hands and a slight drop  
18 foot on the right, and I was able to remain a  
19 productive member of society working as a certified  
20 paralegal for 26 years. I enjoyed hiking, camping,  
21 dancing, swimming, et cetera.

22 However, in 2001, I had to retire due to

1 the worsening of my cognitive problems, and in the  
2 past two years, my disability has progressed very  
3 rapidly. MS has taken away my ability to work,  
4 destroyed my finances, destroyed my health, and is  
5 rapidly destroying my ability to remain  
6 independent.

7           Since the worsening of my MS, I have been  
8 on Avonex, Copaxone, oral and I.V. steroids.  
9 Novantrone was not an option for various reasons.  
10 I actually got worse on these therapies. None of  
11 them stopped my attacks, and now I have an overall  
12 decline in strength and coordination. Only Tysabri  
13 stopped my attacks and gave me hope with the  
14 improvement in my symptoms.

15           The issue here is having the option of a  
16 choice, which we currently do not have without  
17 Tysabri. The FDA's over-caution is not warranted  
18 here. It is only hindering our hopes of a recovery  
19 and a future.

20           Regarding PML, most well-informed patients  
21 know that Tysabri is safe as a monoclonal therapy,  
22 and we have taken steps to clear our bodies of

1 medications in anticipation of Tysabri's return.

2 As a Tysabri patient, I would be more than  
3 willing to undergo regular medical testing  
4 including MRIs and a regular blood test to minimize  
5 any possible risk of PML. These are our bodies and  
6 our lives, and the unmet medical needs of the MS  
7 patients are staggering. There is a much greater  
8 risk presented by not having Tysabri available to  
9 us as a choice.

10 Give us back the right to make our own  
11 fully informed choice and give us back the tools to  
12 do so. Put Tysabri back in the arsenal of  
13 therapies to choose from.

14 I gratefully thank you for this  
15 opportunity to address the AC panel. I pray that  
16 you never have to experience this dreadful  
17 debilitating disease called multiple sclerosis. Do  
18 the right thing and give us Tysabri back now until  
19 something better comes along.

20 Thank you.

21 MS. FUQUAY: My name is Carol Keller  
22 Fuquay. I have had primary progressive MS for over

1 30 years. It is the most severe form of the  
2 disease, and there are no disease-modifying drugs  
3 at all to treat it.

4 I am speaking to you on video because it  
5 is difficult for me to travel. I have been in a  
6 wheelchair since 1995, and in 2001, I lost function  
7 in my right hand. My disease was moving quickly,  
8 and in 2004, I became a full-fledged quadriplegic.

9 I had two Tysabri infusions when the drug  
10 was available, and I feel that it helped me. I can  
11 still speak and swallow, and I hope Tysabri will be  
12 available soon, so that I have the best possible  
13 chance to retain these valuable functions.

14 Please bring Tysabri back, so that it will  
15 be available for all who need it.

16 Thank you for your valuable time.

17 MR. RICHARDSON: My name is Charlie  
18 Richardson. For full disclosure, I have absolutely  
19 no financial interest in any pharmaceutical company  
20 including the ones involved here.

21 I was diagnosed in 1988. I have had a  
22 relapsing and progressive course ever since then.

1 I have been in a wheelchair for about three years.

2 I am sort of a classic non-responder. I have gone  
3 through therapy with all the popular drugs.

4 Betaseron treatments produced nothing but  
5 bad side reactions, spiking liver enzymes and  
6 continued relapses. Avonex, the persistent flu  
7 symptoms and chemical depression was too much to  
8 handle, even with single dose and double dose both  
9 tried.

10 Mitoxantrone, and multiple steroid  
11 treatments have given me incredible osteoporosis  
12 that I now have to treat with parathyroid hormone  
13 injections. I tried IVIG and it gave me an  
14 anaphylactic reaction on the second dose.

15 Nothing has stopped the relapsing and the  
16 progression.

17 I may be stable today, but as you can see,  
18 I am a Kurtzke 8, I don't want to become a Kurtzke  
19 9, and what I would like to do is to have all the  
20 options on the table. Let my neurologist and I  
21 decide what the risk and benefit ratios are. It  
22 may turn out that Tysabri has limits to its

1 duration of use where recommendation is to get one  
2 dose a year. More experience is necessary in order  
3 to be able to determine that.

4 MS is not a monolithic disease. I would  
5 like to advocate with the people, the researchers  
6 that are here, that there is some effort being made  
7 to determine what the subgroups are and responders  
8 and non-responders to MS drugs.

9 I believe that as a biostatistician that  
10 you can certainly stratify by HLA markers and by  
11 MRI type whether you have T1-hypointense gadolinium  
12 enhancing lesions. You certainly ought to be able  
13 to stratify the data in order to be able to get  
14 more information about which patient subgroups  
15 respond to these drugs and which ones don't.

16 In my biostatistic lectures, I often say  
17 and teach that, quote, "Given enough opportunity,  
18 uncommon things happen commonly, but not  
19 specifically."

20 There is 1 in 1,000 chance of developing  
21 MS. After winning that lottery, I am fully  
22 prepared to be one of the 999 out of the 1,000

1 patients who don't develop PML when taking Tysabri.

2 Thank you for your consideration.

3 MS. KUTLER: My name is Alison Kutler. I  
4 am not sponsored by any organization. I was  
5 diagnosed with MS almost 12 years ago at the age of  
6 23. I have relapsing-remitting MS, which manifests  
7 in intermittent exacerbations and a wide array of  
8 baseline symptoms which have increased  
9 significantly over time.

10 I am an attorney at a large law firm,  
11 which sometimes requires long hours. I also  
12 exercise intensely six days per week, and I am an  
13 avid tennis player. I maintain an active social  
14 life and travel frequently for both business and  
15 pleasure, and I serve on the board and work daily  
16 to expand a national nonprofit organization which  
17 provides recreational opportunities to severely  
18 disabled children.

19 My days begin at 5:00 a.m. and oftentimes  
20 run well into the evening as I try to balance the  
21 many things on my plate. I participated in the  
22 Tysabri combination trial. As you are aware, the

1 first phase was complete after 26 months, and the  
2 second phase was open-label with the option to  
3 discontinue Avonex, which I did.

4 I was on Tysabri alone for five months  
5 before the drug was withdrawn. I started taking  
6 interferons nine years ago and have remained on the  
7 therapy without any breaks beyond the five months  
8 of the clinical trial.

9 Although I am a big believer in the  
10 interferons positive impact in limiting my  
11 exacerbations and slowing my disease progression,  
12 it has resulted in a significant decrease in my  
13 quality of life as I have severe side effects which  
14 last for 48 hours each week.

15 The challenges presented by being sick two  
16 days out of every week, but continuing to lead an  
17 active and productive life are great. Imagine  
18 having one chance at a meeting with a member of  
19 Congress to advocate your client's position with a  
20 burning fever, or attending your father's surprise  
21 65th birthday party with a headache so bad you  
22 cannot even see straight, or playing a big doubles

1 match with aches and chills throughout your body.

2           During the five months that I was on  
3 Tysabri alone, I felt terrific. My baseline  
4 symptoms all but disappeared, and I did not have  
5 any exacerbations, and I had two days of each week  
6 returned to my life.

7           I also had the comfort of knowing that I  
8 was on a drug that is profoundly more effective  
9 than any of the other medicines available. It was  
10 an amazing five months in all respects.

11           I would like to commend the FDA for its  
12 quick action and would urge the committee to make  
13 the recommendation to bring Tysabri back to the  
14 marketplace. I believe that patients, in  
15 conjunction with their doctor, should be given the  
16 opportunity to conduct a risk-benefit analysis for  
17 their individual situation.

18           I have closely reviewed the available data  
19 over the past year, as well as the recently  
20 released reports in the New England Journal of  
21 medicine, which clearly suggest to me that Tysabri  
22 is an incredibly effective drug and the risk is

1 manageable at this time.

2           There will be a growing body of knowledge  
3 regarding the drug's effectiveness and the  
4 potential causes of PML, and my ongoing  
5 decision-making process will continue to take this  
6 new information into account.

7           I would also urge the committee to make  
8 Tysabri available to newly diagnosed patients and  
9 others, such as myself, who have worked hard over  
10 time to limit disease progression. I think it  
11 would be the absolute wrong approach to make  
12 Tysabri only available as a last resort to patients  
13 who have not had success with other treatments and  
14 who have more severe progression.

15           The best advantage to Tysabri is that it  
16 may be able to slow disease progression to prevent  
17 thousands of patients from developing more severe  
18 and debilitating cases of MS that will diminish  
19 their abilities to be healthy and productive  
20 members of society.

21           Thank you for the opportunity to testify.

22           MRS. MILLER: Good afternoon. Thank you

1 for allowing us to speak today. Neither my husband  
2 nor I have any financial interest in, nor have we  
3 received any financial help in being here.

4 My name is Karen Miller. I have multiple  
5 sclerosis. What you should also know about me is  
6 that I do not take risks easily. I floss daily, I  
7 buy products with the Consumer Reports Seal of  
8 Approval. I intentionally overpay my estimated  
9 taxes. I drink milk only after double-checking the  
10 sell by date. And I want to take Tysabri again.

11 I would prefer not to risk coming here to  
12 speak publicly. I would prefer not to risk being  
13 in a drug trial with--and I quote from the standard  
14 consent form--"Risk including the possibility of  
15 death and side effects not currently known."

16 I would prefer not to risk having PML.  
17 So, why, in order to speak here for two and a half  
18 minutes, would I spend three days resting, have my  
19 husband work on my muscles and tendons from 3:00  
20 a.m. to 7:00 a.m. this morning, and risk the next  
21 weeks bedridden?

22 Why, on November 4th, 1997, did I consent

1 to be the 32nd human being to participate in the  
2 early Phase II trial for what was then called the  
3 Antegren?

4 Why, on February 28th, 2005, did I spend  
5 \$15,000 from my savings to buy bottles of a drug  
6 that was being removed from the market?

7 So, why would I take Tysabri and why would  
8 I be here today? To help the medical science of  
9 multiple sclerosis, to aid the MS population, to  
10 have a chance to teach legal ethics again, to take  
11 a shower without anybody nearby in case I fall, to  
12 swallow confident that I will not choke on my own  
13 saliva, to read and to remember, to feel my niece's  
14 hug.

15 Yes, there is risk, but with the medical  
16 information from my wise and caring neurologist,  
17 Dr. William Sheremata, and with the support of my  
18 husband and family, with prayer, I took Tysabri in  
19 1997 and again in 2004, 2005, and I will do  
20 everything I possibly can for those who want to,  
21 and for myself, to have the chance to take it  
22 again.

1 Off Tysabri, on a good day, I am a 5.5 on  
2 the disability scale, on my crutches for about 10  
3 feet, facing chemotherapy.

4 On Tysabri, it's a whole new day. I am a  
5 1.5 on the EDSS scale. I have been on my bike for  
6 10 miles facing the road ahead.

7 MR. MILLER: My name is David Miller. For  
8 the last eight years I have looked at Tysabri  
9 through three different lenses: as a former  
10 business executive, now as a pastor, a theologian,  
11 and a Professor of Business Ethics at Yale Divinity  
12 School and Yale School of Management, and most  
13 importantly, as the husband and caregiver of a  
14 woman with MS.

15 As a former business person, I want  
16 companies to develop and make a good profit. As a  
17 pastor, a theologian, and an ethicist, I raise  
18 questions of justice, compassion, and integrity.

19 Finally, as a husband of 26 years, and now  
20 a caregiver, every day my wife is without Tysabri I  
21 see her ability to function running out like sand  
22 granules in an hourglass. Without Tysabri, she is

1 at greater risk of ending up in a wheelchair and  
2 becoming a cognitive shell of the women she once  
3 was. This is real risk.

4 I have this image. I enter an  
5 old-fashioned bank and walk up to the counter.  
6 Behind the inch-thick bullet glass stands a doctor  
7 in a white lab coat. In front of him is a small  
8 glass vial of Tysabri. The doctor does nothing. I  
9 shout, asking for the Tysabri. "I will pay  
10 anything," I weep. He does nothing. I am not sure  
11 if he can hear me. I pound against the glass,  
12 trying to get it to break to get at the vial. Of  
13 course, the glass window is bulletproof and the  
14 shield easily withstands my blows. But finally,  
15 the doctor moves and reaches for the vial, and the  
16 question is will he break through the glass barrier  
17 or will he turn away.

18 Let me show you another piece of glass,  
19 this small, triangle glass was once part of the  
20 North Tower of the World Trade Center in New York.  
21 I had the privilege to serve as a chaplain at  
22 Ground Zero for nine months.

1           Early one morning as we left the pit to go  
2 to the morgue, a fireman gave this chard of glass,  
3 this once clear, strong, impenetrable glass.  
4 Imagine people like you and me, that morning  
5 peacefully looking out their window, out that  
6 glass. Suddenly the planes hit and this glass  
7 shattered as did their lives.

8           I am reminded by these images that nothing  
9 in life is fully safe or 100 percent risk-free.  
10 Not the bulletproof windows in an old bank, not the  
11 impenetrable glass from the North Tower, and not  
12 even exciting new advances in medicine.

13           Too often all we do is sweep up the broken  
14 glass of our life, but today, you, you have the  
15 rare privilege to break through a barrier for the  
16 good, and restore thereby the shattered chards of  
17 our lives - not just for my wife, but also for the  
18 countless others impacted by this invidious  
19 disease.

20           Please return Tysabri to the market.

21           I thank you.

22           MS. SALES: Hi. My name is Barbara Sales.

1 I am from Raleigh, North Carolina. I have no  
2 affiliation with any company. I am here on my own  
3 behalf.

4 I was diagnosed with relapsed-remitting MS  
5 in March of 2000. I am a pediatric nurse and was  
6 able to work until February of 2003. At that  
7 point, my most significant symptoms were extreme  
8 fatigue and migraine headaches for three years.

9 I had tried numerous prescription and  
10 over-the-counter medications with no relief. I  
11 even went as far as having Botox injections and  
12 sinus surgery. I participated in a double-blind  
13 drug study starting August 25th, 2003, and  
14 continued on Tysabri with my daily injections of  
15 Copaxone until the Tysabri was taken off the  
16 market. My last dose was on February 21st, 2005.

17 I found out I was on the Tysabri during  
18 the study, after the drug was pulled from the  
19 market. I had done very well on the Tysabri with  
20 no side effects or exacerbations.

21 From August 25th, 2003, until February  
22 21st, 2005, while I was on the Tysabri, I had an

1 average of 5.3 headaches per month over 19 months  
2 compared to daily headaches before that, and the  
3 fatigue was noticeably improved.

4 Since stopping the Tysabri, there has been  
5 an increase in my headaches and fatigue. The  
6 headaches have increased to 6.6 per month, and I  
7 now have daily headaches continuously since  
8 December of 2005.

9 I am hopeful that all we learn from new  
10 medications, there will be a cure in my lifetime,  
11 and I am requesting that Tysabri be brought back on  
12 the market and let the patient and their physician  
13 decide if this drug is the drug of choice in  
14 treating their MS.

15 Thank you.

16 MS. SMITH: Good afternoon. My name is  
17 Heather Smith. I am 36 years old and live in  
18 Indiana. I was diagnosed with MS in 1998. In full  
19 disclosure, I bought 100 shares of Biogen stock  
20 after realizing that Tysabri was a miracle drug. I  
21 also provide my views as an MS patient to Biogen on  
22 an advisory panel as a volunteer.

1           Today, you will hear requests, such as  
2    please return Tysabri to MS patients, let patients  
3    evaluate their own risk versus quality of life.

4           I, too, am motivated by these requests and  
5    bring them to you as my own, but as I sit here,  
6    because I cannot stand for the duration of my  
7    allotted time, I am motivated by other requests  
8    that I hear every day, requests, such as "You dance  
9    with me, mamma", "You chase me now, mamma", "You  
10   carry me, please."

11           These requests from my son, Ezra, that I  
12   cannot fulfill are the key to my risk-benefit  
13   equation. In the five short years since my  
14   diagnosis, I became disabled. I struggle to walk  
15   with the help of a walker. I am constantly  
16   fatigued and I am incontinent.

17           I have taken Avonex and Rebif while  
18   watching my disease progress. These drugs were  
19   obviously failing me, yet, out of fear and lack of  
20   alternatives, I continued these shots, waiting for  
21   a new choice.

22           That choice came in January of '05, when I

1 received my first infusion of Tysabri. After only  
2 one dose, I felt that Tysabri was a miracle for me.  
3 I was able to make outings on my own. My mobility  
4 drastically improved, and I transitioned from my  
5 walker back to using a cane.

6 The best reward was that I had more energy  
7 to spend with my son. By my second infusion, in  
8 February of '05, I started to focus on my future.  
9 I no longer had to budget my energy and choose  
10 between playing with Ezra or taking a shower. I  
11 could freely enjoy each moment of his life with a  
12 renewed hope.

13 On March 1st of '05, my hopes vanished and  
14 my MS has continued to progress. Interferons were  
15 not helping me, so I began taking Copaxone. I am  
16 no longer able to drive, I cannot go anywhere  
17 unassisted.

18 With all this considered, my risk-benefit  
19 analysis is quite clear. I know Tysabri worked for  
20 me when all other MS drugs failed. Each MS patient  
21 has the right to make an informed choice and create  
22 their own risk-benefit analysis. Each patient will

1 have a different equation and a different answer at  
2 different stages of their life.

3           It is easy for me to see that five years  
4 ago, I would not have taken Tysabri. I would have,  
5 however, lived with a greater peace of mind knowing  
6 that there was another choice available for me when  
7 I was ready and my need for benefits outweighed the  
8 risks.

9           I may never be able to carry my son, Ezra,  
10 or chase him, or dance with him, but he deserves a  
11 mom that is as healthy as possible. Each day  
12 without Tysabri is a day without hope, a day closer  
13 to my permanent disability.

14           DR. WADE: Good afternoon. I would like  
15 to thank the committee for allowing me to speak  
16 today. I have a consulting agreement and speak on  
17 a speakers program for Biogen Idec. I speak for  
18 Serono. I speak for the makers of Copaxone, Teva,  
19 and I also speak for Berlex.

20           I have approximately 150 MS patients that  
21 I follow in my office. In the fall of '05, I began  
22 to treat MS patients with Tysabri and treated about

1 15 patients. My patients found the medicine very,  
2 very effective. I have one patient that found she  
3 was able to get up and clean her house for the  
4 first time in four years. She can't take any of  
5 the interferons, she has depression, and she has  
6 skin reactions to Copaxone therapy.

7 With the withdrawal of this medication  
8 from the market, there was a significant amount of  
9 despair in my patients. They again had to live  
10 more with the fear of the next exacerbation, about  
11 getting worse on this disease.

12 I live with the same fear. I had optic  
13 neuritis when I was in college. I developed  
14 intranuclear ophthalmic plegia, had double vision  
15 in medical school, and was diagnosed with multiple  
16 sclerosis.

17 I was treated a little bit of low-dose  
18 prednisone, but it didn't do much, but I did  
19 recover enough to complete medical school and  
20 started internal medicine training. During that  
21 time, I had a significant exacerbation where I  
22 couldn't walk for a month. I was home in bed.

1 I recovered, finished my medicine  
2 training, and went on to training in Neurology. In  
3 Neurology, I had another significant exacerbation  
4 and back home in bed, but took intravenous  
5 Solu-Medrol and got better in a week.

6 I completed my training and started in  
7 practice in Hartford, Connecticut in 1990. I have  
8 had several exacerbations over the time. One in  
9 the mid-1990s left me so that it wasn't all better.  
10 I finally took my head out of the sand and said I  
11 might as well take one of these medicines.

12 I took a daily injection medication  
13 because it seemed easiest. I found after taking  
14 that medicine for about a year and a half I had  
15 another attack, and at the end of the month, there  
16 was about 10 doses left in the refrigerator,  
17 because taking a shot every day reminds me I am  
18 sick every day, and I try to deny being sick.

19 I switched to weekly interferon injections  
20 and have taken that medicine on a regular basis. I  
21 have had one attack in the past four years.

22 Unfortunately, I have flu-like reactions

1 for two to three days after every injection. I am  
2 still not feeling well today. I take the  
3 injections on Sunday.

4 When Tysabri came out, I took three doses  
5 of the medication and then it was withdrawn from  
6 the market. I am back on weekly interferon  
7 therapy, back having flu-like reactions. My  
8 patients and I live in fear of the next attack,  
9 live in fear of losing my ability to help my  
10 patients, to be with my family.

11 I understand there is a risk to taking  
12 Tysabri, but there is a real risk to not taking it,  
13 having more attacks, and getting worse and worse  
14 and worse and worse.

15 I have a great deal of empathy for all the  
16 patients that have spoken here today. I understand  
17 how they feel. I am asking this committee to allow  
18 me to treat my patients with this very, very  
19 effective therapy.

20 Thank you.

21 MS. GREENFIELD: My name is Audrey  
22 Greenfield and I am 49 years old. I have no ties,

1 financial or otherwise, to either Elan or Biogen  
2 Idec.

3 I was the girl who had everything - ivy  
4 league education, successful career as a real  
5 estate partner in a prestigious law firm, beautiful  
6 family, and multiple sclerosis.

7 This insidious disease that progresses  
8 daily has robbed me of almost everything I once  
9 had. Even my choice for treatment has been taken  
10 away from me. I am appearing here today as my own  
11 advocate to have my right of choice restored to me.

12 I have always been proactive when it came  
13 to deciding on a course of treatment for my MS. I  
14 have tried all available treatments - Novantrone,  
15 Cytosan, cladribine, methotrexate, steroids, IVIG,  
16 the ABC drugs, and Rebif.

17 With each of these treatments, my doctor  
18 required me to have monthly blood tests, periodic  
19 liver and kidney function tests, EKGs, and MRIs.  
20 Unfortunately, the side effects with each treatment  
21 were debilitating, and for what. There was not one  
22 bit of improvement in my level of disability or in

1 the progression of my disease.

2 Then, I heard about Tysabri. I discussed  
3 it with my doctor, who said the drug was well  
4 tolerated in clinical trials. In January 2005, my  
5 health insurance provider pre-approved payment for  
6 12 treatments of Tysabri. I had my first and only  
7 infusion in February 2005. Then, the drug was  
8 pulled from the market.

9 I had no adverse reactions or side  
10 effects. I was even able to ride the bus home on  
11 my own after treatment. That alone was a huge step  
12 forward for me in this disease.

13 It has been over a year now and I haven't  
14 had any treatments of any kind because nothing has  
15 worked for me. I feel as if I am losing my battle  
16 against MS. I have no other options. Without  
17 Tysabri I don't even have hope.

18 I have no illusions. Tysabri was never  
19 marketed or hailed as a cure for MS, however, the  
20 clinical trials proved conclusively that the drug  
21 halted the progression of the disease and, in some  
22 cases, lessened the degree of disability.

1           It is wrong to think that MS is not a  
2 life-threatening disease. My quality of life is  
3 threatened every day that I go without a treatment  
4 that I deserve.

5           My daughter is graduating from high school  
6 in June. Before I know it, she will be getting  
7 married.

8           I would like the chance to halt the  
9 progression of my disease and walk down the aisle  
10 with her. Please allow me the chance to see if  
11 Tysabri can make my dream come true.

12           MR. FRANKLIN: Good afternoon and thank  
13 you for the very important work you are doing on  
14 this subject today.

15           I am Doug Franklin. I am the President  
16 and CEO of the Multiple Sclerosis Association of  
17 America.

18           We were founded in 1970. For 35 years, we  
19 have had only one goal, and that is to help people  
20 deal with this dreaded disease. All of our efforts  
21 are aimed at the patient and their care partners.  
22 That is all we do.

1           Our mission is to enrich the quality of  
2   life for individuals with MS. We receive funding  
3   support for some of our services in public  
4   education outreach from pharmaceutical companies.  
5   We support the FDA position that all currently  
6   approved MS drugs have value for MS patients.

7           We speak to all of our patients about all  
8   of the therapies. Informed consumer consent is our  
9   objective. The funding we receive from  
10   pharmaceutical companies makes up less than 10  
11   percent of our total funding. We receive no  
12   government funding. The remaining 90 percent comes  
13   from the public through donations, through gifts,  
14   through special event fund-raising.

15           We remain a strong neutral advocate for  
16   patient education, and we are very pleased to be  
17   able to be here today to respond, to be able to  
18   share our views on the reintroduction of the drug  
19   Tysabri.

20           When I say "we," I am speaking for MSAA.  
21   I am speaking for the charity, our Healthcare  
22   Advisory Council, our board of directors, and in

1 particular, our Chief Medical Officer, Dr. Jack  
2 Burkes, who had to leave today.

3 Dr. Burkes is a clinical Professor of  
4 Medicine, of Neurology, at the University of  
5 Nevada, School of Medicine. He is also a member of  
6 the Medical Advisory Board of the National MS  
7 Society. He has edited two textbooks on multiple  
8 sclerosis, and in the 1970s, he established the  
9 Rocky Mountain MS Center in Colorado, one of the  
10 nation's first comprehensive MS centers.

11 His input into this brief today represents  
12 MSAA's thoughts. He believes people's lives are at  
13 stake and he has been serving MS patients for more  
14 than 30 years.

15 We all know this drug was approved for the  
16 treatment of relapsing-remitting MS and released  
17 into the marketplace in November of 2004. In our  
18 winter edition of our quarterly newsletter, The  
19 Motivator, Dr. Burkes had the following to say in  
20 the Ask the Doctor section.

21 He said discussing the role of Tysabri  
22 with your doctor is an excellent idea. Only one

1 year data is available on adding Tysabri to Avonex  
2 and no data is available for combining Tysabri with  
3 Betaseron, Copaxone, or Rebif.

4 Tysabri plus Avonex was more effective  
5 than Avonex plus placebo at one year in a group of  
6 patients on Avonex who were having attacks or new  
7 MRI activity. In my opinion, this is a very  
8 selected group of patients, may not be relevant to  
9 Copaxone or high-dosed interferons. More studies  
10 are needed before the effectiveness and/or  
11 potential complications of combination therapy  
12 using Tysabri are known.

13 Two months later, the drug was voluntarily  
14 suspended, and based on reports of the dramatic  
15 events that we are all well aware of, including the  
16 events in Anita Smith's death.

17 The MSAA welcomes the development of newer  
18 and more effective medications to treat MS, but we  
19 believe great care must be exercised when bringing  
20 a new drug with potential serious side effects to  
21 market.

22 In our experience, most of our MS patients

1 do very well on currently available medications  
2 with minimal side effects in the long run  
3 especially if started on treatment early in their  
4 disease course.

5           As a charity, we struggle with the concept  
6 of a possible black box warning label sufficing as  
7 a caution to physicians and patients. Caveat  
8 emptor, buyer beware seems to run contrary to sound  
9 medical treatment based on first do no harm  
10 principles.

11           We strongly believe that patient safety  
12 must be a primary consideration as the FDA proceeds  
13 with the process of analyzing all of the available  
14 data. If Tysabri is reintroduced, precautions  
15 should be taken to protect the patient until  
16 long-term safety can be evaluated.

17           These include strong scientifically-based  
18 protocols to ensure the patient's understanding of  
19 the treatments versus the risk-benefits. This can  
20 be problematic.

21           Can this be assured if more than 50  
22 percent of patients have cognitive dysfunction,

1 which includes reduced executive function, which  
2 may make it difficult to completely understand the  
3 consequences of decisions?

4 Two issues predominant are patients'  
5 perspectives on Tysabri, the relative strength of  
6 the drug over current treatments and toxicity.  
7 Many patients are convinced that Tysabri is twice  
8 as effective as any other treatment available  
9 today.

10 For example, a website  
11 mspatientsforchoice.org has developed a positive  
12 portrait of the benefits of Tysabri over currently  
13 available treatments. Does the FDA agree with  
14 these conclusions? This type of information will  
15 likely become accepted by MS patients who are  
16 always looking for the cure.

17 We need the FDA's position on relative  
18 efficacy. Who more credible than the FDA to  
19 address these issues?

20 Also, the MS patient's risk of PML are  
21 perceived as rare. Counter to this, we hear  
22 concerns of 1 in 1,000 death rates associated with

1 this. What is the truth? Are there potential  
2 risks other than PML, cancers or infections? Can  
3 PML be detected before damaging the brain? Dr.  
4 Burkes insists that by the time PML is detected,  
5 every single cell in the brain has been affected.

6 MS. CANAVAN: Hello. My name is Marcy  
7 Canavan. I have no ties, financial or otherwise,  
8 to any drug company.

9 I led a pretty charmed life up until a few  
10 years ago. Then, one day MS hit me with a bang.  
11 Within two months of the initial attack, I couldn't  
12 walk across my yard. In less than a year I was  
13 using a scooter, retired on disability, and drove  
14 my car with hand controls.

15 I have taken Solu-Medrol many, many times,  
16 Betaseron, Copaxone, methotrexate, and finally,  
17 Novantrone. That was the only drug that helped.  
18 The fast downhill spiral stopped, and I actually  
19 improved, but I have exhausted my lifetime limit.

20 The downhill spiral is starting again. I  
21 risked congestive heart failure and leukemia to  
22 take the Novantrone. Before the Novantrone, aside

1 from the physical problems, I had very serious  
2 cognitive difficulties. I stopped reading anything  
3 because by sentence two, I couldn't remember what  
4 sentence one said anymore.

5 My memory disappeared. I found myself  
6 forgetting where I was, where I was going, and how  
7 to get where I had been on decades. I can't tell  
8 you how many times I just sat on the beltway lost.  
9 Simple words eluded me. My IQ dropped 25 points,  
10 and that was before I hit bottom.

11 My reason for being here today is simple.  
12 I have no treatment options left, and at the rate I  
13 am losing ground again, in a few years, my life  
14 won't be worth living.

15 I am willing to take a chance on a drug  
16 that shows as much promise as Tysabri, and  
17 according to the data you have in front of you, it  
18 is much safer than the one I have already taken  
19 anyway.

20 When I was a kid, I had my life saved  
21 twice by drugs, once when I had blood poisoning and  
22 once with pneumonia. Those same two drugs almost

1 killed me as an adult, when I had full-blown  
2 anaphylactic shock attacks after taking them.

3 Am I mad because the FDA approved a drug  
4 that nearly killed me? No. If you hadn't approved  
5 them, I wouldn't be here at all today anyway.

6 The risk of death is not a reason to deny  
7 a desperately needed drug. What you have to do is  
8 weigh the risk of the death against the need for  
9 the drug.

10 I want to see my grandson grow up. I  
11 would rather be able to enjoy things now and take a  
12 chance that I won't live that long than miss  
13 enjoying life and live to be 100. Quality is  
14 important, and it is more important than quantity.  
15 That applies to lots of things, but especially to  
16 life.

17 I ask you to approve Tysabri for me, for  
18 the other people here, but even more for my  
19 daughter, Emily, who has already spoken to you  
20 today. Compared to her, I still lead a charmed  
21 life. I was 46 when MS hit me. She was 24. All  
22 of her plans and hopes for a life are in shambles

1 thanks to MS.

2           Several days a week, she is in bed all day  
3 because of intractable pain. She has all the same  
4 problems I do, and she is only 27 years old. I had  
5 a normal life for 25 years after finishing school.  
6 She had a normal one for 4 months. I want Tysabri  
7 badly, but for my baby, I want it desperately.

8           You have the power to give her a chance,  
9 and I would ask you to do it. When you make your  
10 decision, please think about how you would feel if  
11 Emily was your child.

12           DR. KIEBURTZ: I thank all the speakers  
13 who have spoken so far. We are going to take a  
14 15-minute break before we go on with the rest of  
15 the speakers.

16           We will reconvene right at 3 o'clock.

17           [Break.]

18           DR. KIEBURTZ: We will begin the open  
19 public hearing now, please.

20           MR. CROYDON: Good afternoon. My name is  
21 Stan Croydon. No one has paid for me to be here  
22 today, and I have no financial interests in any

1 drug companies. They, however, have a whole lot of  
2 my money and a big interest in me keeping using  
3 their medications.

4 Before I left home this morning, my wife  
5 said to me, "Why are you speaking today? You never  
6 took that drug." I said, "You are right, but if  
7 someday I or my doctors think I should be taking  
8 it, I want that option. I want people to know that  
9 we are the ones who ought to making the decisions  
10 on the pros and cons of medication."

11 I have had multiple sclerosis symptoms  
12 since 1967. For the mathematically challenged, that  
13 is 39 years, but it took me eight years to get an  
14 accurate diagnosis. Then, it was one made by a  
15 psychiatrist who I was seeing. I had gone to my  
16 regular doctor one visit, and said give me the  
17 names of a good psychiatrist and a good  
18 neurologist. One of those two has to have the  
19 answer to what is wrong with me.

20 Guess what. He gave me the name of his  
21 psychiatrist.

22 Well, back in 1975, steroids were about

1 the only thing available to help a person with MS,  
2 and when I took mine for the first time, I felt  
3 like I was walking around with my finger plugged  
4 into a light socket. I also began to worry that I  
5 might wind up pumping iron or even worse by the  
6 time I got finished taking those drugs. Ever since  
7 I have tried to avoid those.

8 It was a decade ago I first learned how to  
9 give myself a daily subcutaneous shot of Copaxone,  
10 but when my insurance company looked at the fine  
11 print of what my doctor had written, they realize I  
12 had the wrong kind of MS to be taking that drug.

13 Consequently, I had to switch to Avonex  
14 three months later, and instead of giving me those  
15 shots, I decided to let the nurses at work give me  
16 my weekly intramuscular injections for the next  
17 seven years.

18 Today, I am using Rebif at the  
19 recommendation of another MS patient who is a nurse  
20 and an expert in her field. She saw improvement in  
21 her condition after taking that subcutaneous  
22 medication, and my doctor concurred with my

1 decision to change.

2 I like to think of myself as a well  
3 educated medication consumer. I ask my doctor  
4 plenty of questions about the course of my MS, ask  
5 for an MRI if I feel I need it, and he thinks I am  
6 getting better, and if I hear about new therapies,  
7 I go and investigate them.

8 I even read the sheets you get at the  
9 pharmacy that come with your medications. I have  
10 been doing that ever since one neurologist  
11 prescribed an antidepressant for me when I told him  
12 I was depressed. I called him back three days  
13 later and said, "I have stopped your drug." I  
14 said, "When I first came to see you, I was  
15 depressed, now, I am impotent, and frankly, I would  
16 rather be depressed."

17 [Laughter.]

18 MS. TIBURTIUS: Good afternoon. My name  
19 is Bartira. I was diagnosed with a mass in March  
20 2001. I was on the Tysabri starting combination  
21 with Avonex for 28 months. In the past, I did some  
22 educational programs coordinated by Biogen. The

1 company paid for my expenses and my time. I spoke  
2 about my experience with MS, not about Biogen  
3 drugs. Biogen did not encourage or pay for me to  
4 be here today.

5 I am a language teacher and I need to be  
6 alert all the time, but four years ago, I had two  
7 very bad relapses that put me in the hospital. I  
8 had all the symptoms in the book including loss of  
9 vision, and the worst of all, I had cognition  
10 problem.

11 I can handle everything even a wheelchair,  
12 if I have to, but I cannot handle to lose the  
13 ability of thinking, and I had some very bad  
14 cognition problem.

15 I was switching letters, I had difficulty  
16 remembering simple words. I was getting lost in  
17 conversation. I used to wake up in the morning and  
18 not having a clue where I was. I was spacing out.  
19 I didn't know if I was dreaming or it was a  
20 reality. I was confused between where reality and  
21 a dream. I was like a nightmare.

22 When I start on the Tysabri study, it was

1 a double-blinded study, but it seems the first  
2 infusion, I was so sure that I was getting the real  
3 thing, not the placebo because the way I was  
4 feeling. Little by little I started to feel  
5 healthier and healthier.

6 The fatigue was gone, I had my brain back  
7 100 percent, but a couple months ago, I started to  
8 have problems again. The fatigue is back, my left  
9 arm is numb, my face is numb, and again sometimes I  
10 cannot remember simple words.

11 I am very scared. I am a teacher. I  
12 cannot afford to lose the ability of thinking  
13 again. I don't want to go back there. I want to  
14 be able to walk, to speak, eat and drink, and the  
15 most important, I want to be able to think. I want  
16 to know when I am dreaming or when I am awake.

17 I do understand that there is a small risk  
18 with Tysabri, but the risk that I am willing to  
19 take. If someone tells me that Tysabri is going to  
20 take 10 years off of my life, but I will have the  
21 quality of life I had a year ago when I was in the  
22 study, I would take it.

1 financial or otherwise, to either Elan or Biogen  
2 Idec.

3 I was the girl who had everything - ivy  
4 league education, successful career as a real  
5 estate partner in a prestigious law firm, beautiful  
6 family, and multiple sclerosis.

7 This insidious disease that progresses  
8 daily has robbed me of almost everything I once  
9 had. Even my choice for treatment has been taken  
10 away from me. I am appearing here today as my own  
11 advocate to have my right of choice restored to me.

12 I have always been proactive when it came  
13 to deciding on a course of treatment for my MS. I  
14 have tried all available treatments - Novantrone,  
15 Cytoxan, cladribine, methotrexate, steroids, IVIG,  
16 the ABC drugs, and Rebif.

17 With each of these treatments, my doctor  
18 required me to have monthly blood tests, periodic  
19 liver and kidney function tests, EKGs, and MRIs.  
20 Unfortunately, the side effects with each treatment  
21 were debilitating, and for what. There was not one  
22 bit of improvement in my level of disability or in

1 the progression of my disease.

2 Then, I heard about Tysabri. I discussed  
3 it with my doctor, who said the drug was well  
4 tolerated in clinical trials. In January 2005, my  
5 health insurance provider pre-approved payment for  
6 12 treatments of Tysabri. I had my first and only  
7 infusion in February 2005. Then, the drug was  
8 pulled from the market.

9 I had no adverse reactions or side  
10 effects. I was even able to ride the bus home on  
11 my own after treatment. That alone was a huge step  
12 forward for me in this disease.

13 It has been over a year now and I haven't  
14 had any treatments of any kind because nothing has  
15 worked for me. I feel as if I am losing my battle  
16 against MS. I have no other options. Without  
17 Tysabri I don't even have hope.

18 I have no illusions. Tysabri was never  
19 marketed or hailed as a cure for MS, however, the  
20 clinical trials proved conclusively that the drug  
21 halted the progression of the disease and, in some  
22 cases, lessened the degree of disability.

1           It is wrong to think that MS is not a  
2   life-threatening disease. My quality of life is  
3   threatened every day that I go without a treatment  
4   that I deserve.

5           My daughter is graduating from high school  
6   in June. Before I know it, she will be getting  
7   married.

8           I would like the chance to halt the  
9   progression of my disease and walk down the aisle  
10   with her. Please allow me the chance to see if  
11   Tysabri can make my dream come true.

12           MR. FRANKLIN: Good afternoon and thank  
13   you for the very important work you are doing on  
14   this subject today.

15           I am Doug Franklin. I am the President  
16   and CEO of the Multiple Sclerosis Association of  
17   America.

18           We were founded in 1970. For 35 years, we  
19   have had only one goal, and that is to help people  
20   deal with this dreaded disease. All of our efforts  
21   are aimed at the patient and their care partners.  
22   That is all we do.

1           Our mission is to enrich the quality of  
2   life for individuals with MS. We receive funding  
3   support for some of our services in public  
4   education outreach from pharmaceutical companies.  
5   We support the FDA position that all currently  
6   approved MS drugs have value for MS patients.

7           We speak to all of our patients about all  
8   of the therapies. Informed consumer consent is our  
9   objective. The funding we receive from  
10   pharmaceutical companies makes up less than 10  
11   percent of our total funding. We receive no  
12   government funding. The remaining 90 percent comes  
13   from the public through donations, through gifts,  
14   through special event fund-raising.

15           We remain a strong neutral advocate for  
16   patient education, and we are very pleased to be  
17   able to be here today to respond, to be able to  
18   share our views on the reintroduction of the drug  
19   Tysabri.

20           When I say "we," I am speaking for MSAA.  
21   I am speaking for the charity, our Healthcare  
22   Advisory Council, our board of directors, and in

1 particular, our Chief Medical Officer, Dr. Jack  
2 Burkes, who had to leave today.

3 Dr. Burkes is a clinical Professor of  
4 Medicine, of Neurology, at the University of  
5 Nevada, School of Medicine. He is also a member of  
6 the Medical Advisory Board of the National MS  
7 Society. He has edited two textbooks on multiple  
8 sclerosis, and in the 1970s, he established the  
9 Rocky Mountain MS Center in Colorado, one of the  
10 nation's first comprehensive MS centers.

11 His input into this brief today represents  
12 MSAA's thoughts. He believes people's lives are at  
13 stake and he has been serving MS patients for more  
14 than 30 years.

15 We all know this drug was approved for the  
16 treatment of relapsing-remitting MS and released  
17 into the marketplace in November of 2004. In our  
18 winter edition of our quarterly newsletter, The  
19 Motivator, Dr. Burkes had the following to say in  
20 the Ask the Doctor section.

21 He said discussing the role of Tysabri  
22 with your doctor is an excellent idea. Only one

1 year data is available on adding Tysabri to Avonex  
2 and no data is available for combining Tysabri with  
3 Betaseron, Copaxone, or Rebif.

4 Tysabri plus Avonex was more effective  
5 than Avonex plus placebo at one year in a group of  
6 patients on Avonex who were having attacks or new  
7 MRI activity. In my opinion, this is a very  
8 selected group of patients, may not be relevant to  
9 Copaxone or high-dosed interferons. More studies  
10 are needed before the effectiveness and/or  
11 potential complications of combination therapy  
12 using Tysabri are known.

13 Two months later, the drug was voluntarily  
14 suspended, and based on reports of the dramatic  
15 events that we are all well aware of, including the  
16 events in Anita Smith's death.

17 The MSAA welcomes the development of newer  
18 and more effective medications to treat MS, but we  
19 believe great care must be exercised when bringing  
20 a new drug with potential serious side effects to  
21 market.

22 In our experience, most of our MS patients

1 do very well on currently available medications  
2 with minimal side effects in the long run  
3 especially if started on treatment early in their  
4 disease course.

5 As a charity, we struggle with the concept  
6 of a possible black box warning label sufficing as  
7 a caution to physicians and patients. Caveat  
8 emptor, buyer beware seems to run contrary to sound  
9 medical treatment based on first do no harm  
10 principles.

11 We strongly believe that patient safety  
12 must be a primary consideration as the FDA proceeds  
13 with the process of analyzing all of the available  
14 data. If Tysabri is reintroduced, precautions  
15 should be taken to protect the patient until  
16 long-term safety can be evaluated.

17 These include strong scientifically-based  
18 protocols to ensure the patient's understanding of  
19 the treatments versus the risk-benefits. This can  
20 be problematic.

21 Can this be assured if more than 50  
22 percent of patients have cognitive dysfunction,

1 which includes reduced executive function, which  
2 may make it difficult to completely understand the  
3 consequences of decisions?

4 Two issues predominant are patients'  
5 perspectives on Tysabri, the relative strength of  
6 the drug over current treatments and toxicity.  
7 Many patients are convinced that Tysabri is twice  
8 as effective as any other treatment available  
9 today.

10 For example, a website  
11 mspatientsforchoice.org has developed a positive  
12 portrait of the benefits of Tysabri over currently  
13 available treatments. Does the FDA agree with  
14 these conclusions? This type of information will  
15 likely become accepted by MS patients who are  
16 always looking for the cure.

17 We need the FDA's position on relative  
18 efficacy. Who more credible than the FDA to  
19 address these issues?

20 Also, the MS patient's risk of PML are  
21 perceived as rare. Counter to this, we hear  
22 concerns of 1 in 1,000 death rates associated with

1 this. What is the truth? Are there potential  
2 risks other than PML, cancers or infections? Can  
3 PML be detected before damaging the brain? Dr.  
4 Burkes insists that by the time PML is detected,  
5 every single cell in the brain has been affected.

6 MS. CANAVAN: Hello. My name is Marcy  
7 Canavan. I have no ties, financial or otherwise,  
8 to any drug company.

9 I led a pretty charmed life up until a few  
10 years ago. Then, one day MS hit me with a bang.  
11 Within two months of the initial attack, I couldn't  
12 walk across my yard. In less than a year I was  
13 using a scooter, retired on disability, and drove  
14 my car with hand controls.

15 I have taken Solu-Medrol many, many times,  
16 Betaseron, Copaxone, methotrexate, and finally,  
17 Novantrone. That was the only drug that helped.  
18 The fast downhill spiral stopped, and I actually  
19 improved, but I have exhausted my lifetime limit.

20 The downhill spiral is starting again. I  
21 risked congestive heart failure and leukemia to  
22 take the Novantrone. Before the Novantrone, aside

1 from the physical problems, I had very serious  
2 cognitive difficulties. I stopped reading anything  
3 because by sentence two, I couldn't remember what  
4 sentence one said anymore.

5 My memory disappeared. I found myself  
6 forgetting where I was, where I was going, and how  
7 to get where I had been on decades. I can't tell  
8 you how many times I just sat on the beltway lost.  
9 Simple words eluded me. My IQ dropped 25 points,  
10 and that was before I hit bottom.

11 My reason for being here today is simple.  
12 I have no treatment options left, and at the rate I  
13 am losing ground again, in a few years, my life  
14 won't be worth living.

15 I am willing to take a chance on a drug  
16 that shows as much promise as Tysabri, and  
17 according to the data you have in front of you, it  
18 is much safer than the one I have already taken  
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20 When I was a kid, I had my life saved  
21 twice by drugs, once when I had blood poisoning and  
22 once with pneumonia. Those same two drugs almost

1 killed me as an adult, when I had full-blown  
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14 important, and it is more important than quantity.  
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18 the other people here, but even more for my  
19 daughter, Emily, who has already spoken to you  
20 today. Compared to her, I still lead a charmed  
21 life. I was 46 when MS hit me. She was 24. All  
22 of her plans and hopes for a life are in shambles

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7 badly, but for my baby, I want it desperately.

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9 and I would ask you to do it. When you make your  
10 decision, please think about how you would feel if  
11 Emily was your child.

12 DR. KIEBURTZ: I thank all the speakers  
13 who have spoken so far. We are going to take a  
14 15-minute break before we go on with the rest of  
15 the speakers.

16 We will reconvene right at 3 o'clock.

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18 DR. KIEBURTZ: We will begin the open  
19 public hearing now, please.

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21 Stan Croydon. No one has paid for me to be here  
22 today, and I have no financial interests in any

1 drug companies. They, however, have a whole lot of  
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5 said to me, "Why are you speaking today? You never  
6 took that drug." I said, "You are right, but if  
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13 is 39 years, but it took me eight years to get an  
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15 psychiatrist who I was seeing. I had gone to my  
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11 advocate to have my right of choice restored to me.

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9   progression of my disease and walk down the aisle  
10   with her. Please allow me the chance to see if  
11   Tysabri can make my dream come true.

12           MR. FRANKLIN: Good afternoon and thank  
13   you for the very important work you are doing on  
14   this subject today.

15           I am Doug Franklin. I am the President  
16   and CEO of the Multiple Sclerosis Association of  
17   America.

18           We were founded in 1970. For 35 years, we  
19   have had only one goal, and that is to help people  
20   deal with this dreaded disease. All of our efforts  
21   are aimed at the patient and their care partners.  
22   That is all we do.

1           Our mission is to enrich the quality of  
2 life for individuals with MS. We receive funding  
3 support for some of our services in public  
4 education outreach from pharmaceutical companies.

5 We support the FDA position that all currently  
6 approved MS drugs have value for MS patients.

7           We speak to all of our patients about all  
8 of the therapies. Informed consumer consent is our  
9 objective. The funding we receive from  
10 pharmaceutical companies makes up less than 10  
11 percent of our total funding. We receive no  
12 government funding. The remaining 90 percent comes  
13 from the public through donations, through gifts,  
14 through special event fund-raising.

15           We remain a strong neutral advocate for  
16 patient education, and we are very pleased to be  
17 able to be here today to respond, to be able to  
18 share our views on the reintroduction of the drug  
19 Tysabri.

20           When I say "we," I am speaking for MSAA.  
21 I am speaking for the charity, our Healthcare  
22 Advisory Council, our board of directors, and in

1 particular, our Chief Medical Officer, Dr. Jack  
2 Burkes, who had to leave today.

3 Dr. Burkes is a clinical Professor of  
4 Medicine, of Neurology, at the University of  
5 Nevada, School of Medicine. He is also a member of  
6 the Medical Advisory Board of the National MS  
7 Society. He has edited two textbooks on multiple  
8 sclerosis, and in the 1970s, he established the  
9 Rocky Mountain MS Center in Colorado, one of the  
10 nation's first comprehensive MS centers.

11 His input into this brief today represents  
12 MSAA's thoughts. He believes people's lives are at  
13 stake and he has been serving MS patients for more  
14 than 30 years.

15 We all know this drug was approved for the  
16 treatment of relapsing-remitting MS and released  
17 into the marketplace in November of 2004. In our  
18 winter edition of our quarterly newsletter, The  
19 Motivator, Dr. Burkes had the following to say in  
20 the Ask the Doctor section.

21 He said discussing the role of Tysabri  
22 with your doctor is an excellent idea. Only one

1 year data is available on adding Tysabri to Avonex  
2 and no data is available for combining Tysabri with  
3 Betaseron, Copaxone, or Rebif.

4 Tysabri plus Avonex was more effective  
5 than Avonex plus placebo at one year in a group of  
6 patients on Avonex who were having attacks or new  
7 MRI activity. In my opinion, this is a very  
8 selected group of patients, may not be relevant to  
9 Copaxone or high-dosed interferons. More studies  
10 are needed before the effectiveness and/or  
11 potential complications of combination therapy  
12 using Tysabri are known.

13 Two months later, the drug was voluntarily  
14 suspended, and based on reports of the dramatic  
15 events that we are all well aware of, including the  
16 events in Anita Smith's death.

17 The MSAA welcomes the development of newer  
18 and more effective medications to treat MS, but we  
19 believe great care must be exercised when bringing  
20 a new drug with potential serious side effects to  
21 market.

22 In our experience, most of our MS patients

1 do very well on currently available medications  
2 with minimal side effects in the long run  
3 especially if started on treatment early in their  
4 disease course.

5 As a charity, we struggle with the concept  
6 of a possible black box warning label sufficing as  
7 a caution to physicians and patients. Caveat  
8 emptor, buyer beware seems to run contrary to sound  
9 medical treatment based on first do no harm  
10 principles.

11 We strongly believe that patient safety  
12 must be a primary consideration as the FDA proceeds  
13 with the process of analyzing all of the available  
14 data. If Tysabri is reintroduced, precautions  
15 should be taken to protect the patient until  
16 long-term safety can be evaluated.

17 These include strong scientifically-based  
18 protocols to ensure the patient's understanding of  
19 the treatments versus the risk-benefits. This can  
20 be problematic.

21 Can this be assured if more than 50  
22 percent of patients have cognitive dysfunction,

1 which includes reduced executive function, which  
2 may make it difficult to completely understand the  
3 consequences of decisions?

4 Two issues predominant are patients'  
5 perspectives on Tysabri, the relative strength of  
6 the drug over current treatments and toxicity.  
7 Many patients are convinced that Tysabri is twice  
8 as effective as any other treatment available  
9 today.

10 For example, a website  
11 mspatientsforchoice.org has developed a positive  
12 portrait of the benefits of Tysabri over currently  
13 available treatments. Does the FDA agree with  
14 these conclusions? This type of information will  
15 likely become accepted by MS patients who are  
16 always looking for the cure.

17 We need the FDA's position on relative  
18 efficacy. Who more credible than the FDA to  
19 address these issues?

20 Also, the MS patient's risk of PML are  
21 perceived as rare. Counter to this, we hear  
22 concerns of 1 in 1,000 death rates associated with

1 this. What is the truth? Are there potential  
2 risks other than PML, cancers or infections? Can  
3 PML be detected before damaging the brain? Dr.  
4 Burkes insists that by the time PML is detected,  
5 every single cell in the brain has been affected.

6 MS. CANAVAN: Hello. My name is Marcy  
7 Canavan. I have no ties, financial or otherwise,  
8 to any drug company.

9 I led a pretty charmed life up until a few  
10 years ago. Then, one day MS hit me with a bang.  
11 Within two months of the initial attack, I couldn't  
12 walk across my yard. In less than a year I was  
13 using a scooter, retired on disability, and drove  
14 my car with hand controls.

15 I have taken Solu-Medrol many, many times,  
16 Betaseron, Copaxone, methotrexate, and finally,  
17 Novantrone. That was the only drug that helped.  
18 The fast downhill spiral stopped, and I actually  
19 improved, but I have exhausted my lifetime limit.

20 The downhill spiral is starting again. I  
21 risked congestive heart failure and leukemia to  
22 take the Novantrone. Before the Novantrone, aside

1 from the physical problems, I had very serious  
2 cognitive difficulties. I stopped reading anything  
3 because by sentence two, I couldn't remember what  
4 sentence one said anymore.

5 My memory disappeared. I found myself  
6 forgetting where I was, where I was going, and how  
7 to get where I had been on decades. I can't tell  
8 you how many times I just sat on the beltway lost.  
9 Simple words eluded me. My IQ dropped 25 points,  
10 and that was before I hit bottom.

11 My reason for being here today is simple.  
12 I have no treatment options left, and at the rate I  
13 am losing ground again, in a few years, my life  
14 won't be worth living.

15 I am willing to take a chance on a drug  
16 that shows as much promise as Tysabri, and  
17 according to the data you have in front of you, it  
18 is much safer than the one I have already taken  
19 anyway.

20 When I was a kid, I had my life saved  
21 twice by drugs, once when I had blood poisoning and  
22 once with pneumonia. Those same two drugs almost

1 killed me as an adult, when I had full-blown  
2 anaphylactic shock attacks after taking them.

3 Am I mad because the FDA approved a drug  
4 that nearly killed me? No. If you hadn't approved  
5 them, I wouldn't be here at all today anyway.

6 The risk of death is not a reason to deny  
7 a desperately needed drug. What you have to do is  
8 weigh the risk of the death against the need for  
9 the drug.

10 I want to see my grandson grow up. I  
11 would rather be able to enjoy things now and take a  
12 chance that I won't live that long than miss  
13 enjoying life and live to be 100. Quality is  
14 important, and it is more important than quantity.  
15 That applies to lots of things, but especially to  
16 life.

17 I ask you to approve Tysabri for me, for  
18 the other people here, but even more for my  
19 daughter, Emily, who has already spoken to you  
20 today. Compared to her, I still lead a charmed  
21 life. I was 46 when MS hit me. She was 24. All  
22 of her plans and hopes for a life are in shambles

1 thanks to MS.

2           Several days a week, she is in bed all day  
3 because of intractable pain. She has all the same  
4 problems I do, and she is only 27 years old. I had  
5 a normal life for 25 years after finishing school.  
6 She had a normal one for 4 months. I want Tysabri  
7 badly, but for my baby, I want it desperately.

8           You have the power to give her a chance,  
9 and I would ask you to do it. When you make your  
10 decision, please think about how you would feel if  
11 Emily was your child.

12           DR. KIEBURTZ: I thank all the speakers  
13 who have spoken so far. We are going to take a  
14 15-minute break before we go on with the rest of  
15 the speakers.

16           We will reconvene right at 3 o'clock.

17           [Break.]

18           DR. KIEBURTZ: We will begin the open  
19 public hearing now, please.

20           MR. CROYDON: Good afternoon. My name is  
21 Stan Croydon. No one has paid for me to be here  
22 today, and I have no financial interests in any

1 drug companies. They, however, have a whole lot of  
2 my money and a big interest in me keeping using  
3 their medications.

4 Before I left home this morning, my wife  
5 said to me, "Why are you speaking today? You never  
6 took that drug." I said, "You are right, but if  
7 someday I or my doctors think I should be taking  
8 it, I want that option. I want people to know that  
9 we are the ones who ought to making the decisions  
10 on the pros and cons of medication."

11 I have had multiple sclerosis symptoms  
12 since 1967. For the mathematically challenged, that  
13 is 39 years, but it took me eight years to get an  
14 accurate diagnosis. Then, it was one made by a  
15 psychiatrist who I was seeing. I had gone to my  
16 regular doctor one visit, and said give me the  
17 names of a good psychiatrist and a good  
18 neurologist. One of those two has to have the  
19 answer to what is wrong with me.

20 Guess what. He gave me the name of his  
21 psychiatrist.

22 Well, back in 1975, steroids were about

1 the only thing available to help a person with MS,  
2 and when I took mine for the first time, I felt  
3 like I was walking around with my finger plugged  
4 into a light socket. I also began to worry that I  
5 might wind up pumping iron or even worse by the  
6 time I got finished taking those drugs. Ever since  
7 I have tried to avoid those.

8 It was a decade ago I first learned how to  
9 give myself a daily subcutaneous shot of Copaxone,  
10 but when my insurance company looked at the fine  
11 print of what my doctor had written, they realize I  
12 had the wrong kind of MS to be taking that drug.

13 Consequently, I had to switch to Avonex  
14 three months later, and instead of giving me those  
15 shots, I decided to let the nurses at work give me  
16 my weekly intramuscular injections for the next  
17 seven years.

18 Today, I am using Rebif at the  
19 recommendation of another MS patient who is a nurse  
20 and an expert in her field. She saw improvement in  
21 her condition after taking that subcutaneous  
22 medication, and my doctor concurred with my

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1 decision to change.

2 I like to think of myself as a well  
3 educated medication consumer. I ask my doctor  
4 plenty of questions about the course of my MS, ask  
5 for an MRI if I feel I need it, and he thinks I am  
6 getting better, and if I hear about new therapies,  
7 I go and investigate them.

8 I even read the sheets you get at the  
9 pharmacy that come with your medications. I have  
10 been doing that ever since one neurologist  
11 prescribed an antidepressant for me when I told him  
12 I was depressed. I called him back three days  
13 later and said, "I have stopped your drug." I  
14 said, "When I first came to see you, I was  
15 depressed, now, I am impotent, and frankly, I would  
16 rather be depressed."

17 [Laughter.]

18 MS. TIBURTIUS: Good afternoon. My name  
19 is Bartira. I was diagnosed with a mass in March  
20 2001. I was on the Tysabri starting combination  
21 with Avonex for 28 months. In the past, I did some  
22 educational programs coordinated by Biogen. The

1 company paid for my expenses and my time. I spoke  
2 about my experience with MS, not about Biogen  
3 drugs. Biogen did not encourage or pay for me to  
4 be here today.

5 I am a language teacher and I need to be  
6 alert all the time, but four years ago, I had two  
7 very bad relapses that put me in the hospital. I  
8 had all the symptoms in the book including loss of  
9 vision, and the worst of all, I had cognition  
10 problem.

11 I can handle everything even a wheelchair,  
12 if I have to, but I cannot handle to lose the  
13 ability of thinking, and I had some very bad  
14 cognition problem.

15 I was switching letters, I had difficulty  
16 remembering simple words. I was getting lost in  
17 conversation. I used to wake up in the morning and  
18 not having a clue where I was. I was spacing out.  
19 I didn't know if I was dreaming or it was a  
20 reality. I was confused between where reality and  
21 a dream. I was like a nightmare.

22 When I start on the Tysabri study, it was

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1 a double-blinded study, but it seems the first  
2 infusion, I was so sure that I was getting the real  
3 thing, not the placebo because the way I was  
4 feeling. Little by little I started to feel  
5 healthier and healthier.

6 The fatigue was gone, I had my brain back  
7 100 percent, but a couple months ago, I started to  
8 have problems again. The fatigue is back, my left  
9 arm is numb, my face is numb, and again sometimes I  
10 cannot remember simple words.

11 I am very scared. I am a teacher. I  
12 cannot afford to lose the ability of thinking  
13 again. I don't want to go back there. I want to  
14 be able to walk, to speak, eat and drink, and the  
15 most important, I want to be able to think. I want  
16 to know when I am dreaming or when I am awake.

17 I do understand that there is a small risk  
18 with Tysabri, but the risk that I am willing to  
19 take. If someone tells me that Tysabri is going to  
20 take 10 years off of my life, but I will have the  
21 quality of life I had a year ago when I was in the  
22 study, I would take it.

1           If I have Tysabri back, I will have life.  
2   If I don't, I don't even know if I am going to have  
3   a future.

4           Thank you for listening.

5           DR. GODEC: I am Dr. Mark Godec, a  
6   physician in private practice in the Washington,  
7   D.C. area. I have no financial interest in Biogen  
8   and Elan, and I have not received financial support  
9   from any competing companies.

10          I would like to thank the committee for  
11   the opportunity to speak today.

12          Anita Smith was a healthy, active woman  
13   until her final months and untimely death from PML  
14   arising from Tysabri therapy. She was the wife of  
15   Walter Smith and the mother of two children.

16          She worked daily in her family's business  
17   and lived a full life without restriction or  
18   disability. At the request of Walter Smith, I  
19   reviewed Anita Smith's medical records. She was in  
20   good health until June 1999, when she developed  
21   minimal neurological symptoms that were eventually  
22   attributed to multiple sclerosis.

1           However, the medical evaluation that led  
2   to the diagnosis of MS was incomplete and produced  
3   results that were not diagnostic of MS. At most,  
4   only her presenting episode provided objective  
5   clinical evidence of a CNS lesion that might be due  
6   to MS.

7           An MRI of her brain revealed only a small  
8   number of nonspecific lesions that did not enhance  
9   with gadolinium. Her CSF never showed oligoclonal  
10   bands that are characteristic of MS.

11          EP studies were not performed and she was  
12   not evaluated by a neuro-ophthalmologist. Her  
13   symptoms were mild and her EDSS score remained  
14   between zero and 2, indicating that she had no  
15   significant disability. At most, she should have  
16   been considered to have possible MS.

17          Despite a questionable diagnosis of MS,  
18   Biogen and Elan enrolled Ms. Smith into the  
19   Sentinel study in April 2002. It is likely Biogen  
20   and Elan offered substantial monetary awards to  
21   physicians for each patient they enrolled in the  
22   study.

1           Biogen and Elan reported in the New  
2   England Journal of Medicine that Ms. Smith's  
3   enrollment MRI showed nine lesions consistent with  
4   MS to justify her enrollment in the study. This  
5   enrollment MRI actually shows only four or five  
6   nonspecific lesions per Dr. Greg Shoukimas, who you  
7   heard earlier today.

8           In November 2004, Ms. Smith developed much  
9   more serious neurological signs and symptoms.  
10   Tysabri was eventually discontinued, but her  
11   condition continued to deteriorate.

12           Anita Smith tragically died on February  
13   24th, 2005, from PML at the age of 46.  
14   Neuropathological examination of her brain and  
15   spinal cord revealed only PML lesions, and no MS  
16   plaques, verifying that she did not have MS.

17           Had Biogen and Elan not inappropriately  
18   enrolled her in the Sentinel study, she would be  
19   alive today.

20           Ms. Smith's case dramatically demonstrates  
21   the danger of Tysabri therapy. As a physician, I  
22   would like to see effective and safe drugs

1 available to all MS patients. Unfortunately,  
2 Tysabri is not the miracle drug for MS that  
3 everyone is hoping for. Returning Tysabri to the  
4 market will only put more people's lives in  
5 jeopardy.

6 I strongly encourage this committee to  
7 carefully consider the risk that Tysabri poses to  
8 the public. Despite the recent clearance Tysabri  
9 received for human clinical trials, I strongly  
10 believe that Biogen and Elan should be required to  
11 conduct additional animal studies to fully define  
12 Tysabri's safety before it is again given to  
13 humans.

14 Thank you very much.

15 MS. ROGERS: Hello. Thank you for the  
16 opportunity to testify before you today. My name  
17 is Martha Rogers and I just turned 53 years old. I  
18 am a wife, a mother of two teenage daughters, and a  
19 teacher working 30 hours a week, and I have MS.

20 I was once asked to speak about Avonex and  
21 was paid \$300, but I am here today on my own to  
22 speak about my experiences with Tysabri. My world

1 as I knew it changed two years ago, when I was 50,  
2 and initially diagnosed with MS.

3 At that time, I was happy, working full  
4 time, getting into shape and feeling great. Every  
5 day was a joy to live, and I was thankful. I was  
6 diagnosed in February 2004, after an attack of  
7 optic neuritis, which my doctor first thought was a  
8 brain tumor.

9 An MRI showed my condition to be multiple  
10 sclerosis. My neurologist allowed me to choose  
11 Avonex, because I felt that that was the best  
12 disease-altering drug for me. At that time, I was  
13 also encouraged about the news of future release of  
14 Tysabri. I think they called it Antegren at that  
15 time.

16 My first relapse occurred in the spring of  
17 2004. I was one of the very first patients in the  
18 Norfolk area to receive an infusion of Tysabri in  
19 January 2005. I was so excited about going on this  
20 drug, and I knew it was so important that I was  
21 able to get two local TV stations to film me  
22 getting my infusion.

1 I received two infusions and felt  
2 fantastic within 24 hours of my infusion. I knew  
3 the drug was working. I knew that I could face any  
4 obstacle with this disease as long as I had my  
5 Tysabri. My fatigue went away, I felt steadier on  
6 my feet, and my concentration improved.

7 Since February 2005, when the drug was  
8 pulled from the market, my MS has progressed and I  
9 have had three more relapses. My symptoms have  
10 returned and I have gone on steroid therapy. I  
11 have had to adjust my life in many ways in order to  
12 manage the various symptoms of this devastating and  
13 unpredictable disease.

14 My particular symptoms include balance and  
15 gait issues, constant fatigue, memory and  
16 concentration problems, impaired vision, and  
17 depression. I have also had to cut back on my  
18 hours at work, which has been causing my family  
19 financial difficulties.

20 The progression of my disease has consumed  
21 my thoughts, challenging me to overcome my anger of  
22 having MS.

1 I urge you to consider the results, the  
2 clinical results proving that Tysabri can have a  
3 profound ability to stop MS. I believe that this  
4 drug can prevent my disease from getting any worse.  
5 It's all about maintaining a quality of life.

6 I believe Tysabri is the best drug  
7 available today for people like me.

8 Thank you.

9 MR. KELLER: Thank you for your time  
10 today. I have received no financial support or  
11 interest in any of these pharmaceutical companies  
12 in question today or competitors.

13 My name is Larry Keller and I would like  
14 to tell you about my sister, Carol Keller Fuquay.  
15 For about 30 years, Carol has had MS, the most  
16 progressive kind of MS. We witnessed her testimony  
17 during the second video here earlier before the  
18 break.

19 Being her younger brother, I have always  
20 looked up to Carol as the model of success. She  
21 completed her Bachelor's Degree after only three  
22 years of study, followed with a Master's in

1 computer science, and became one of the first  
2 female project engineers at Hewlett-Packard in the  
3 early 1970s.

4 Carol has always been at the forefront of  
5 technology, has been blessed with a supportive  
6 family, but at the point in her business and family  
7 careers, where she should have been most active,  
8 she noticed the muscles in her legs weren't  
9 responding the way she expected. Yes, she was  
10 experiencing the onset of MS.

11 The reason I tell you this story is that  
12 my sister, after having poured her energies into a  
13 successful career, redirected them to find out  
14 everything she could about this debilitating  
15 disease. At that time, no one even knew the cause  
16 of MS.

17 Over the next three decades, she learned  
18 everything she could about the current research  
19 into the disease, she came to know many of the  
20 nation's leading MS researchers, neurologists, and  
21 immunologists.

22 She learned, as they discovered, the

1 causes of the disease, but the cure remained  
2 elusive. Over the last 15 years, she tried every  
3 imaginable treatment, even a hyperbaric chamber,  
4 all in an effort to arrest the progression of her  
5 MS. None of these were truly successful.

6 Over time, she lost the use of her legs,  
7 then, her right arm and hand, then, finally, her  
8 left. If only she could stabilize the progression  
9 of her MS. She fears the next step is that she  
10 will lose the ability to speak and swallow. You  
11 can imagine her long-term prognosis.

12 However, during this slow decline, she  
13 decided to share this knowledge she acquired on MS  
14 and help others who have been unable to converse  
15 with those at the forefront of research. She  
16 decided to offer this knowledge in a book, which  
17 she published last year, "Understanding MS Builds  
18 Hope." You can imagine the difficulty she had  
19 trying to put this together in the condition that  
20 you witnessed on the video.

21 During her research, she became aware of  
22 the clinical trials of Tysabri, and once it was

1 approved for use in late 2004, she was able to  
2 receive two treatments prior to the drug's removal.  
3 As Carol has always been a close monitor of her  
4 condition, she noticed that during the year of  
5 2005, she experienced no progression of her MS.

6 This is quite exceptional since she had  
7 had the most severe and progressive form. Tysabri  
8 works for my sister. It has arrested the  
9 progression of her disease.

10 Consider Carol's case, consider her  
11 condition, consider her prognosis. Tysabri is the  
12 only hope she has.

13 I ask, as my sister asks, for the  
14 committee to recommend that Tysabri be returned to  
15 the market. How fitting an end to my sister's book  
16 that not only does understanding MS build hope, but  
17 that there is real hope that we have a cure for  
18 this disease.

19 Thank you.

20 DR. SMITH: Hello. I am David Smith,  
21 Rochester, New York. I am a board-certified  
22 neurologist and neuro-ophthalmologist. I have a

1 private practice and care for several hundred  
2 active MS patients.

3 I would like to speak from my own  
4 experience to you today. I diagnosed my wife's MS  
5 15 years ago.

6 When I go to the meetings, it seems like  
7 the discussion always revolves around the relative  
8 merits of the ABCR drugs, neutralizing antibodies,  
9 and things like that. When I am in the office, I  
10 am saying to a young lady, look, in order to  
11 preserve your quality of life, we have to arrest  
12 your MS, and I am thinking in my own mind that  
13 those ABCR drugs that we have are only about 30  
14 percent effective.

15 Now, there is a spectrum to severity in  
16 MS. There are aggressive cases and there are mild  
17 cases. In my own experience, if you take one of the  
18 the milder cases and put them on any one of the  
19 ABCR drugs, they arrest, and those people go on and  
20 live happily ever after.

21 But most people, I would say about 80  
22 percent will break through and continue to

1 progress. What that means is that it is just a  
2 matter of a few years before those people go into a  
3 wheelchair.

4 So, our goal in treating  
5 relapsing-remitting MS must be to arrest, not to  
6 slow the disease. What I am suggesting is that the  
7 much higher efficacy of Tysabri will allow us to  
8 arrest many more of those aggressive cases that get  
9 away from us now. So, the benefit-to-risk ratio  
10 here becomes enormous. Do you see what I mean?

11 We have never had a benefit-to-risk ratio  
12 in a drug like this before. I was talking to my  
13 wife, Mary, about four years ago. She was having a  
14 crescendo pattern of attacks, three attacks a year,  
15 and she was on steroids all the time. I said,  
16 well, there is this new drug called CellCept out.  
17 She couldn't tolerate Imuran because of  
18 hepatotoxicity. I said it looks like it ought to  
19 work better than Imuran and safer.

20 So, she says, well, what do I have to  
21 lose? And I read her the riot act - lymphoma,  
22 leukemia, sepsis, all kinds of weird infections.

1 She says what do I have to lose, I am going into a  
2 wheelchair now, and at that time, she was talking  
3 to me about the ways that she would take her life  
4 if she went into a wheelchair.

5 Mary hasn't had one attack since on the  
6 CellCept. That is four years without an attack.

7 Thank you.

8 MR. BURROUGHS: I am Frank Burroughs,  
9 President of the Abigail Alliance for Better Access  
10 to Developmental Drugs. We don't take any money  
11 from the pharmaceutical industry. We represent  
12 patients who are fighting for their lives.

13 The Abigail Alliance paid my expenses to  
14 be here today.

15 Before I get to my talk, I just had one  
16 comment, and that is I am a little confused. Was  
17 Speaker No. 32 a patient advocate?

18 Today's issue is yet another example that  
19 patients are not being put first in the drug  
20 development process. By the way, I am sitting  
21 sideways because I can't turn my back on MS  
22 patients.

1           This slide illustrates that there is a 100  
2   percent chance that multiple sclerosis patients  
3   will perish with the ship. Out of what are now  
4   thousands of patients treated in trials with  
5   Tysabri, there are still only three confirmed cases  
6   of PML.

7           The reports vary a bit, but there is  
8   one-tenth of 1 percent chance one of the lifeboats  
9   will sink, one of the lifeboats. Tysabri never  
10   should have been taken off the market. It was a  
11   severe overreaction to the drug safety hysteria  
12   caused by the Vioxx issues, and the overreaction by  
13   the FDA, also, the media, the FDA Advisory  
14   Committees, and certain politicians played a role.

15           Many thousands of MS patients have  
16   progressed and become more disabled as a result of  
17   the overreaction to these mostly false and  
18   ill-considered magnifications of drug safety  
19   concerns.

20           The FDA Advisory Committees have regressed  
21   from a stance that was already too cautious into an  
22   extreme harm the many to protect the very few

1 posture, that simply must be reversed.

2           The people who run the current system must  
3 realize that it should be the individual patient's  
4 decision as to whether or not they get a new  
5 therapy, such as Tysabri, having the current  
6 information about known risks/benefits.

7           The patients, in consultation with their  
8 physicians, should have greater control over how  
9 they fight for their lives. Ask Parkinson's  
10 patient Robert Suthers. Robert and others will tell  
11 you that MS, Parkinson's, and other illnesses can  
12 be a living death.

13           Let me share a huge catastrophe. Please  
14 listen to this. It was in Fortune magazine last  
15 month. Let me share a huge catastrophe due to the  
16 current system of overreaction due to our current  
17 antiquated method of statistical analysis.

18           Launched in 1998, RotoShield was a  
19 lifeboat for millions of children. It was  
20 virtually 100 percent effective in preventing  
21 rotovirus, a deadly diarrhea-causing virus that  
22 leads to 600,000 deaths worldwide a year, mostly in

1 developing countries.

2 Because there was a 2 chance in 10,000  
3 that there was a bowel obstruction, the drug was  
4 pulled off the market at the urging of the FDA and  
5 the Center for Disease Control. The result of that  
6 was that there was not a new--Wyeth dropped the  
7 vaccine--there was not another vaccine on the  
8 market for six years, and 3.6 million children died  
9 worldwide.

10 This is what happens when government,  
11 individuals get in the way of the rights of  
12 patients and overreact to statistics. What's so  
13 incredible about the rotovirus was that they found  
14 there was a statistical error. We have seen that  
15 over and over again.

16 Here is vivid proof of what I am saying  
17 today, and the Abigail Alliance has been saying for  
18 over five years. Every drug the Abigail Alliance  
19 has pushed for earlier access to is now approved by  
20 the FDA. In this case, we have one, like Iressa,  
21 one that has been pulled back, that needs to be  
22 brought forward.

1           Let me leave you with four things that are  
2   so important. FDA and others must understand  
3   patients need to be put first. There is a  
4   difference between an MS patient, a cancer patient,  
5   Parkinson patients, and somebody with an allergy or  
6   arthritis. Contrary to what an FDA Associate  
7   Commissioner said to me in a meeting, there is  
8   clinical pressures involved in this.

9           Thank you very much.

10          MR. MILTON: My name is Clive Milton. I  
11   represent my wife who has had MS for eight years,  
12   cannot be here today. She was part of the Phase  
13   III placebo-controlled, double-blind study for  
14   Tysabri in the Affirm group.

15          My wife had a very serious side effect,  
16   which could probably have been avoided had a series  
17   of simple allergy tests been performed prior to  
18   acceptance in the study.

19          We discovered after she was unblinded from  
20   the study, and without much help from Yale  
21   University School of Medicine or Biogen, that she  
22   was allergic to polysorbate 80, an ingredient that

1 is used in the delivery solution.

2 She is now hypersensitive to anything that  
3 contains polysorbate, and she has been suffering  
4 from intense itching, severe rash over her arms,  
5 back, and scalp, which results in bleeding and loss  
6 of sleep, loss of work, and quality of life for the  
7 past three years since she was involved in the  
8 study.

9 There is no cure to this type of  
10 hypersensitivity and no one knows the effect of the  
11 additional illness on her MS.

12 No one at the Yale University School of  
13 Medicine or Biogen cared to investigate or help her  
14 once she was unblinded from the study. Where was  
15 the protection, care, and treatment that Biogen,  
16 Yale University School of Medicine, and New Haven  
17 Hospital, and the IRB promised to give her?

18 I have several questions. Why has the FDA  
19 allowed polysorbate 80 to be used in an I.V.  
20 solution especially as it is not recommended as an  
21 injectable by at least one of the manufacturers?

22 Polysorbate is also used in Avonex, also

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1 made by Biogen, and as a result, my wife cannot use  
2 this or any other MS medication that may contain  
3 esters of any kind because of the likelihood of  
4 serious adverse reactions.

5 All the information issued by the FDA and  
6 Biogen seems to be looking at the study drug  
7 Tysabri alone or with Avonex, but could it be  
8 possible that the culprit that forced the closure  
9 of the Sentinel study two weeks before the  
10 conclusion of the Phase III stage, and the issues  
11 found in the Affirm study is not caused by either  
12 drug? Has any testing or research been conducted  
13 to rule out the possibility that one or more of the  
14 constituent components used in the delivery  
15 solution may be the problem?

16 Why did Biogen get to review its own data  
17 when Tysabri was removed from the market? There  
18 appears to be a slight conflict of interest here.  
19 The FDA should mandate the use of an independent  
20 body to review such data to avoid potential  
21 cover-ups or bias in reporting and findings.

22 MR. KAHN: I have made many public

1 presentations during my 30-year career as a General  
2 Electric executive, and in the last 20 years, as an  
3 active participant in my local community. Not one  
4 of these presentations was as important to me  
5 personally as this one is today.

6 I am here in my role as the father of a  
7 daughter whose life is at stake. Without access to  
8 Tysabri, her quality of life is rapidly declining.

9 I do not have a relationship or financial  
10 interest with any company involved in this issue,  
11 nor have I accepted any financial help from any  
12 interested party. I am here solely as a father.

13 In 1996, I went with my daughter for the  
14 first time in 30 years to a doctor. When the  
15 neurologist told us that she had MS, I had to ask  
16 him what MS was, because I knew so little about the  
17 disease.

18 In nine years, I have learned a  
19 considerable amount about MS. I have educated  
20 myself through research, listened to dozens of MS  
21 doctors, attended over 100 MS meetings with expert  
22 speakers, I met with many other MS sufferers and

1 caregivers. I have learned much about MS from  
2 riding the roller coaster of the disease along with  
3 my daughter.

4 Eight year ago, I accompanied my daughter  
5 as she walked with great difficulty into a single  
6 infusion, early Phase II trial for Tysabri, and I  
7 was heartened when I saw her walk briskly as she  
8 left the infusion trial.

9 When my daughter took Tysabri, she had MS,  
10 but she was remarkably stronger and had an improved  
11 quality of life. My daughter is unable to tolerate  
12 the other standard therapies, and therefore, she  
13 has no other viable treatment option.

14 When Tysabri has been unavailable, I have  
15 witnessed her painful suffering and have helped to  
16 move her stuck toes, feet, arms, and fingers, and  
17 helped her eat and walk just as I did when she was  
18 a baby. Certainly, I do not need to tell you there  
19 is not a cure for MS. If there were, we would not  
20 be here today. Until there is a cure, patients  
21 have to choose what treatments, if any, to take to  
22 try to alleviate the symptoms and to stem the

1 course of their diseases.

2 If there were an effective drug that was  
3 risk-free, then, we would also not need to be here  
4 today. I understand that your role as the FDA  
5 Advisory Committee is to ascertain the benefits and  
6 risks of a drug, and to communicate that valuable  
7 information to doctors.

8 This then allows the patients to receive  
9 information and advice tailored to their individual  
10 needs from their doctors, and in my daughter's  
11 case, with her permission, it enables me to be a  
12 more informed member of her consultation team.

13 Finally, in my role as a father, I beg you  
14 to allow those suffering from MS, and their  
15 doctors, the freedom to decide whether or not to  
16 use Tysabri.

17 Thank you.

18 MR. CALFEE: I am John Calfee, an  
19 economist at the American Enterprise Institute in  
20 Washington, D.C., an independent research  
21 organization that receives contributions from many  
22 sources including pharmaceutical firms. My views

1 are my own and do not necessarily represent those  
2 of my employer or anyone else.

3 I wish to summarize the results of a  
4 telephone survey of a representative sample of  
5 patients who see neurologists for treatment of  
6 relapsing-remitting MS.

7 The survey was sponsored by Biogen Idec.  
8 I received compensation for designing and launching  
9 the survey, but have not been compensated for  
10 analyzing the results, for writing the paper I  
11 submitted for the record, or for appearing at these  
12 hearings. Biogen Idec did not see my paper, did  
13 not review it until after it had been submitted to  
14 FDA.

15 Survey participants were recruited by  
16 neurologists who appeared on the American Medical  
17 Association's master list, which includes non-AMA  
18 members. The survey was conducted by Roper Public  
19 Affairs.

20 Briefly, here is what we found:

21 Respondents suffered substantial  
22 disability. Fifty-nine percent said fatigue was a

1 major problem, 10 percent use a wheelchair half or  
2 more of the time, one-fourth always or nearly  
3 always use a cane, crutch, or other support, and  
4 two-thirds require support at least occasionally.

5           Only 20 percent had not suffered relapses  
6 in the previous year. Half had suffered one or  
7 more relapses, and a quarter had suffered three or  
8 more.

9           Ninety-seven percent of patients were  
10 currently on drug therapy. Half had switched  
11 drugs, one-third had switched at least twice.  
12 Ninety-five percent or more thought it was very  
13 important to have new drugs that reduce the  
14 frequency of relapse and retard progression in  
15 disability.

16           We specifically asked about balancing  
17 risks and benefits, but we did so without referring  
18 to Tysabri. Approximately 55 percent said they  
19 would definitely or probably use a drug that  
20 significantly reduces frequency of relapse or  
21 retards progression in disability even if the drug  
22 involves a 1 in 1,000 chance of a fatal side

1 effect. One-third said they would definitely or  
2 probably use such a drug with a 1 in 500 chance of  
3 a fatal side effect.

4 We also found that willingness to tolerate  
5 risk was largely unrelated to disability levels.

6 Several questions asked about the roles of  
7 patients, their neurologists, and the FDA.  
8 Seventy-two percent had seen their neurologist at  
9 least four times in the previous two years.  
10 Sixty-three percent said they talk about side  
11 effect more than half the time.

12 Seventy-nine percent said that they and  
13 their physician were equally involved in drug  
14 decisions. Fifty-four percent agreed that the FDA  
15 should tightly control drugs with safety concerns,  
16 but 71 percent said that once the FDA has provided  
17 a warning, patients should be free to decide with  
18 their physician whether to use such drugs.

19 Finally, almost all patients said they  
20 would be willing to visit their neurologist more  
21 often in order to use risky drugs.

22 Thank you.

1 MR. TRIEDMAN: Thank you for the  
2 opportunity to comment on Tysabri. My name is  
3 Steven Triedman. I am from Providence, Rhode  
4 Island, and my wife and I flew down today  
5 specifically for this hearing.

6 We have a relapsing-remitting course of  
7 MS. I have the physical effects, and she gets to  
8 deal with everything else.

9 MS is an insidious disease that affects  
10 not only we, the patients, but our families, our  
11 friends, and everybody else. I have no ties to any  
12 drug companies although I am a very good customer.

13 I participated in the Sentinel study and  
14 was on both Tysabri and Avonex for over two years,  
15 and I continued after that. I lived a normal life  
16 to the point that if I didn't tell someone that I  
17 had MS, they didn't know. I have had MS for 11  
18 years this month. I didn't relapse and I didn't  
19 have any adverse effects.

20 Since I have been off Tysabri, it has been  
21 a difficult year. I have had numerous relapses and  
22 have switched drugs as we try and deal with each

1 step, and I have also had steroids on a regular  
2 basis.

3 I am a graphic designer, so my work, it  
4 has been difficult at times because of my motor  
5 skills and some cognitive issues. This is a  
6 disease that for 10 years, we have been hearing  
7 about drugs, we haven't seen any new drugs besides  
8 the ABC drugs, so this, to us, is a breakthrough  
9 drug, and for someone with MS, four years is an  
10 eternity. It could be four years, it could be six  
11 years until we see another new drug.

12 I have a lot of experience with MS, as  
13 well as access to exceptional information  
14 professional resources. When I was diagnosed with  
15 MS, my uncle was a recently retired, very prominent  
16 neurologist, and I have numerous friends, doctors,  
17 and relatives in the field, and I receive  
18 superlative care I think from my MS team in Boston.  
19 In fact, selfishly, when I saw my doctor here, I  
20 said to my wife, "I think he came for me."

21 They are very proactive in the research.  
22 They believe in this drug, so I believe in this

1 drug. In addition, I chair the board of the MS  
2 Society and serve as representative on the national  
3 board, so I have been to the meetings, I have seen  
4 all of the drug things. I have not seen anything  
5 nor heard anything like Tysabri.

6 I was on the drug for more than two years.  
7 I will continue on the drug if I can get it, and I  
8 would like, and I wish the committee would  
9 recommend, that it be approved, because I think  
10 people that have MS need that opportunity.

11 It's a personal decision whether you go on  
12 the drug or not, but for those that have been on  
13 the drug, and it has been successful, it's a  
14 decision I think they would make.

15 Thank you very much.

16 DR. MOSADDEGH: We are looking for our  
17 last public hearing speaker, George Grafas, if he's  
18 in the audience. Mr. George Grafas.

19 DR. KIEBURTZ: While we are waiting, if he  
20 appears. I just wanted to thank all the open  
21 public hearing speakers for their frank and  
22 heartfelt comments. I don't want anyone to think

1 that by limiting time, we somehow limit the  
2 importance of your comments.

3 The committee is very grateful to everyone  
4 who made so much effort to come here and to speak.  
5 It helps us inform our deliberations of tomorrow.  
6 I apologize to those who couldn't finish their  
7 comments in the time frame allotted.

8 We have some time that remains on the  
9 agenda, especially while we are waiting for our  
10 last speaker. So, if the committee at this time  
11 has questions they want to address to the sponsor  
12 or to the FDA, that were left over from the  
13 morning, we can take some time to do that.

14 Except for the one last speaker, we will  
15 not entertain any other comments in terms of an  
16 open public hearing, and we will not begin  
17 deliberations today, as I alluded to at the  
18 beginning of the day.

19 Does anyone on the committee have a  
20 question that they would like to address to either  
21 the sponsor or the FDA at this point? Dr. Couch.

22 Questions from the Committee

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1 DR. COUCH: Is the panel going to receive  
2 the most updated form of the RiskMAP study? There  
3 were some comments made about the slides were  
4 slightly inaccurate, there were some additional  
5 data. Are we going to get the very latest version  
6 of that by tomorrow morning?

7 DR. WALTON: The RiskMAP has been in  
8 discussions between the company and the agency, and  
9 what you heard were some of the intended changes,  
10 but there was not a completely coherent rewritten  
11 form of it. So, I think that we have given you the  
12 information about the initial plan and the key  
13 questions that we hope for you to be able to  
14 comment on.

15 DR. KIEBURTZ: It will be our job to, in  
16 the absence of a concrete document, present what we  
17 think our opinions are. Dr. Temple.

18 DR. TEMPLE: I actually just wondered  
19 whether there was a copy of the latest version of  
20 the checklist, which, unless I missed it, I  
21 couldn't find anywhere. Dr. Wysowski referred to  
22 having it, so she must have seen it, but I am sure

1 that would be at least of some help to the  
2 committee.

3 DR. BOZIC: I can present it in slide  
4 format.

5 DR. TEMPLE: Well, let me ask the  
6 committee, do you want to see it now or do you want  
7 to see that tomorrow?

8 DR. KIEBURTZ: You can see it tomorrow. I  
9 see a consensus nodding.

10 DR. KATZ: Is it possible to get hard  
11 copies for the committee just to look at this  
12 evening?

13 DR. BOZIC: Yes, we can, yes.

14 DR. KIEBURTZ: Dr. McArthur.

15 DR. MCARTHUR: I would like to go back to  
16 the pathological examination of Patient 1. I would  
17 like to ask Biogen to comment on some of the  
18 questions that are being raised. I initially asked  
19 the question this morning and I would like to know  
20 if there was an independent examination of the  
21 pathology from the first patient.

22 DR. PANZARA: Well, Biogen Idec was not

1 involved in that autopsy in any way. It was  
2 actually done by Dr. DeMasters. The full  
3 description of the autopsy findings were presented  
4 in the New England Journal of Medicine, and the  
5 level of description in there is our understanding  
6 of the pathology.

7 DR. McARTHUR: It would seem to me  
8 absolutely critical since we are talking about  
9 decisions based on three cases of PML, only two of  
10 which were in patients with multiple sclerosis, and  
11 only one of which had autopsy confirmation, that we  
12 need to know as much as possible about the  
13 pathological findings.

14 I am frankly surprised with your answer.

15 DR. PANZARA: Again, part of the process  
16 following the diagnosis in that patient was that  
17 the autopsy was performed at the University of  
18 Colorado where the patient was seen. Biogen Idec  
19 was not actually permitted access to that  
20 information until after the publication of the  
21 articles in the New England Journal of Medicine.

22 Since then, the autopsy material has been

1 provided to Dr. Gene Major at NIH, who has  
2 performed, to my knowledge, some testing on it, and  
3 has confirmed the presence of JC virus by in-situ  
4 hybridization, so that the diagnosis in Gene  
5 Major's opinion confirms the diagnosis of PML.

6 DR. McARTHUR: That's not the question.  
7 The question is whether the patient had multiple  
8 sclerosis, since our entire, or at least a lot of  
9 our discussion today is on whether that case, that  
10 patient had multiple sclerosis. I am not disputing  
11 the fact that the patient had PML. I am raising  
12 the question as to whether the patient had multiple  
13 sclerosis.

14 DR. PANZARA: It is our understanding of  
15 the pathology report that they could not find an MS  
16 plaque in the autopsy of the brain. We do not know  
17 to what level the spinal cord was evaluated for the  
18 presence of MS plaques.

19 I should say that, as you saw the MRI  
20 during the open hearing, the PML developed in the  
21 region of the T2-hyperintense lesions that were  
22 seen on that MRI. Thus, the autopsy, as presented

1 in the New England Journal, states that they could  
2 not find it, but they conceded that the PML could  
3 have occurred in the region of MS lesions, and  
4 thus, could have obscured it.

5 DR. McARTHUR: Not to be argumentative,  
6 but we saw four or five tiny white matter  
7 hyperintensities. The PML lesion was almost a  
8 panhemispheric lesion, so I think it's impossible  
9 to say where that lesion initially began.

10 DR. PANZARA: No, I agree with you on that  
11 point. I just mean to suggest that that was a  
12 panhemispheric lesion that developed for PML, and  
13 that if there were MS lesions there, they could  
14 have been obscured by the PML lesion itself. That  
15 is again from the pathology report and from the  
16 pathologists at Colorado, who have indicated that  
17 fact to us.

18 DR. McARTHUR: So, the obvious next step  
19 is to examine optic nerve and spinal cord in that  
20 case.

21 DR. PANZARA: Again, my understanding is  
22 of the autopsy that was performed, they did not

1 find lesions in the--again, this is from the New  
2 England Journal of Medicine--in the optic nerve or  
3 the spinal cord, but we don't know what level of  
4 analysis was done in terms of number of sections,  
5 et cetera, in the spinal cord.

6 DR. KIEBURTZ: Dr. Goldstein.

7 DR. GOLDSTEIN: We are going to be talking  
8 tomorrow about I guess the risk minimization plan  
9 and the early patient identification. But assuming  
10 that the system as was described is completely  
11 effective, what data are there that early detection  
12 alters PML would alter the disease course?

13 We are putting a lot on detecting these  
14 cases early and stopping the infusion. How do we  
15 know that that is going to alter the disease course  
16 in any way?

17 DR. PANZARA: The best data that exists is  
18 currently in the HIV experience, but it is not  
19 exactly analogous. The other experience is in  
20 transplantation, and the series in transplantation  
21 have been small.

22 There are typically case series of 25, 10

1 to 25 patients, and then a long list of case  
2 reports. That data suggests that when the  
3 immunosuppressant therapies are discontinued, there  
4 can be an improval in survival.

5 Again, the types of agents used there,  
6 obviously not natalizumab, but agents such as  
7 azathioprine, cyclosporine, in those circumstances,  
8 based on the case series that have been done, about  
9 a third of patients survive, and those that did  
10 survive, it was nearly uniformly they had a  
11 decrease in their immunosuppression.

12 That is really the only literature that  
13 exists in this area.

14 DR. KIEBURTZ: Dr. Ricaurte?

15 DR. RICAURTE: I was just going to take up  
16 on the point that Dr. McArthur raised. Regardless  
17 of what the outcome is, the issue seems to be did  
18 the patient have or not MS, and was she  
19 appropriately enrolled in the study, so the  
20 question I have is what will be done in the future,  
21 or was there something that should have been done  
22 in the past to guard against that, or do things

1 have to be changed in order to preclude an error,  
2 if it was an error, in the future.

3 Just comment on the issue of enrollment  
4 and ensuring that appropriate patients are  
5 selected.

6 DR. PANZARA: You are referring to the  
7 risk management program, or in clinical trials, in  
8 what area specifically is your question regarding?

9 DR. RICAURTE: Well, we don't know what  
10 the outcome of this is. In the most liberal form,  
11 I suppose it would be suppose it is approved to go  
12 on the market, how do we, as a committee, gain  
13 assurance that the drug will be appropriately used  
14 in patients, appropriate patients.

15 DR. PANZARA: I am going to turn that over  
16 to Dr. Sandrock.

17 DR. SANDROCK: We rely on our sites to  
18 make the diagnosis. With our advisory committee  
19 and with the FDA, we write protocols. The protocol  
20 required that the patients had relapsing MS for the  
21 McDonald criteria.

22 We also require that patients have cranial

1 MRIs consistent with MS, and we rely on our  
2 investigators, and we go out and we make sure that  
3 the investigators are qualified, and we rely on our  
4 investigators to make the diagnosis and enroll  
5 patients according to the protocol.

6 That patient had, in her history, had an  
7 episode of acute visual loss with documented loss  
8 in visual acuity in one eye. She had an episode of  
9 myelopathy with spasticity in the lowest  
10 extremities. She met clinical criteria for  
11 multiple sclerosis, and she met the protocol  
12 requirements.

13 DR. RICAURTE: Although they were vague,  
14 the history, as I read it, because she also had a  
15 long history of migraine.

16 DR. SANDROCK: Yes, she did.

17 DR. KIEBURTZ: Let me take a little  
18 prerogative.

19 I think it is inevitable that individuals  
20 are misdiagnosed with neurologic diseases. We will  
21 have to factor in, in our decision-making, which,  
22 of course, won't happen until tomorrow, that there

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1 will be some finite level of misdiagnosis. It is  
2 human and unavoidable.

3 I think that is something we will have to  
4 talk about, how to minimize the chance of that  
5 happening. I am not asserting whether it happened  
6 in this circumstance or not.

7 MS. SITCOV: I was just going to ask,  
8 would you concede that it is possible that she was  
9 misdiagnosed and that she was inappropriately put  
10 in the study?

11 DR. SANDROCK: Ma'am, I did not see the  
12 patient, and I don't like to second guess my  
13 colleagues, who actually saw the patient, examined  
14 the patient, found neurologic findings that were  
15 objective, and MS is a clinical diagnosis. It is  
16 not made by MRI scans. It is made by qualified  
17 neurologists. In this case, this was a  
18 board-certified neurologist who saw the patient,  
19 took the history, did the examination, and I don't  
20 like to second guess my colleagues.

21 MS. SITCOV: Well, could you ask the  
22 neurologist who diagnosed the patient? I don't

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1 mean call him up right now, but at some point, find  
2 out the reasons for his diagnosis?

3 DR. SANDROCK: If you are asking me to do  
4 so, I will.

5 MS. SITCOV: Thank you.

6 DR. KIEBURTZ: Other questions for the  
7 sponsor or the FDA at this point?

8 [No response.]

9 DR. KIEBURTZ: This meeting is adjourned  
10 until 8 o'clock tomorrow morning.

11 [Whereupon, the proceedings were adjourned  
12 at 4:00 p.m., to resume at 8:00 a.m., Wednesday,  
13 March 8, 2006.]

14 - - -

## **EXHIBIT 2**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

Volume II

Wednesday, March 8, 2006

Holiday Inn Gaithersburg  
The Ballrooms  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

## PARTICIPANTS

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Sohail Mosaddegh, RPh., Pharm.D., Acting Exec. Sec.

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## P R O C E E D I N G S

## Call to Order and Introductions

DR. KIEBURTZ: Good morning. I think we will get started.

Just a few reminders to the committee, as well as the observers. The open public hearing is over, so the committee members essentially are going to discuss among themselves, that is, the voting and non-voting members of the committee, discuss among themselves the questions that have been proposed to us.

Please, everyone bear in mind that we can specifically ask questions both to the sponsor and to the FDA about additional analyses. In fact, we have some information and follow-up on questions that were posed to both yesterday, so we will get to that shortly.

Just general format, remember it's a discussion, but it is a structured discussion, and I think it will facilitate things if people do not jump in. Let me recognize you, so that we can go in somewhat of an orderly fashion.

If you feel your point will be diminished by waiting, try to look even more urgent towards me or something, but otherwise, try to go in a structured fashion and, for better or worse, I am the one who gets to structure it, so if you don't like it, you can let me know on the break.

Regarding the questions, just bear in mind that in the preamble there, FDA also encourages the Advisory Committee to discuss any other issues that the members believe are relevant to the current submission.

If you do not believe the current questions adequately cover the issues we need to be covering, I would like to know about that earlier rather than later, and I would propose that you tell me that, and then also, to help sharpen your thinking, put in a question, similar to these questions, so if you think there is an issue that hasn't been addressed by the question, write out another question and then just give it to me.

With that preamble, before we commence properly, we need to once again introduce ourselves

and have the reading of the Conflict of Interest Statement.

So, why don't we go clockwise again, please.

DR. JENKINS: Good morning. I am John Jenkins. I am the Director of the Office of New Drugs in the Center for Drug Evaluation and Research at FDA.

DR. TEMPLE: I am Bob Temple. I am Director of the Office of Drug Evaluation I.

DR. KATZ: I am Russ Katz, Director of the Division of Neurology Products.

DR. WALTON: Marc Walton. I am the Deputy Director of the Division of Neurology Products.

DR. McDERMOTT: I am Susan McDermott. I am a clinical reviewer in the Division of Neurology Products.

DR. A. HUGHES: I am Alice Hughes. I am a clinical safety reviewer in the Division of Neurology Products at the FDA>

DR. DAL PAN: I am Gerald Dal Pan, the Director of the Office of Drug Safety at FDA.

DR. M. HUGHES: I am Michael Hughes. I am a committee member. I am Professor of Biostatistics at Harvard University.

DR. COUCH: I am James Couch. I am a committee member. I am Professor and Chair of Neurology, University of Oklahoma Medical School.

DR. MOSADDEGH: I am Sohail Mosaddegh. I am the Acting Executive Secretary for the PCNS Advisory Committee.

DR. KIEBURTZ: I am Karl Kieburtz. I am Professor of Neurology at the University of Rochester and chairing this Advisory Committee.

DR. MCARTHUR: I am Justin McArthur. I am Professor of Neurology at Johns Hopkins University.

MS. SITCOV: I am Cynthia Sitcov. I am the Patient Representative. I have been diagnosed with MS for almost 31 years.

DR. JUNG: I am Lily Jung. I am a neurologist with the Swedish Neuroscience Institute and Clinical Associate Professor at the University of Washington. I am the Consumer Representative on this committee.

DR. SACCO: Ralph Sacco. I am a member of the committee, Professor of Neurology and Epidemiology at Columbia University.

DR. RICAURTE: I am George Ricaurte. I am Associate Professor of Neurology at Johns Hopkins University.

DR. SEJVAR: Jim Sejvar, neurologist and medical epidemiologist with the Centers for Disease Control.

DR. DeKOSKY: Steven DeKosky, Professor and Chair of the Department of Neurology at the University of Pittsburgh.

DR. GOLDSTEIN: Larry Goldstein, Professor of Medicine and Director of the Stroke Center at Duke.

DR. KOSKI: Carol E. Koski, Professor of Neurology, University of Maryland School of Medicine.

DR. PORTER: Roger Porter, Adjunct Professor of Neurology, University of Pennsylvania, Adjunct Professor of Pharmacology at USUHS. I am the non-voting pharma member.

Conflict of Interest Statement

DR. MOSADDEGH: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee's participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), the following participants have been granted full waivers:

Dr. Steven DeKosky for unrelated consulting and speakers bureau activities for a competing firm for which he receives less than \$10,001 per year, and for unrelated activities in a visiting professor program for a university which receives support from a competing firm for which he receives less than \$10,001 per year;

Dr. Karl Kieburtz for consulting on unrelated matters for the sponsor and three competitors. He receives between \$10,001 and \$50,000 per year from the sponsor and less than \$10,001 per year per firm from the competitors;

Dr. Ralph Sacco for consulting on unrelated matters for a competitor for which he receives less than \$10,001 per year;

Dr. Larry Goldstein for serving on an advisory board and steering committee for a competitor regarding unrelated issues for which he receives from \$10,001 to \$50,000 per year and for consulting on unrelated matters for a competitor for which he receives less than \$10,001 per year;

Dr. Lily Jung for serving on a speakers bureau for the sponsor for which she receives from \$10,001 to \$50,000 per year and for serving on speakers bureau for two competitors for which she receives less than \$10,001 per year per firm.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30

of the Parklawn Building.

We would also like to note that Dr. Roger J. Porter has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Porter's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Porter is a retired employee of Wyeth Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. KIEBURTZ: Any updates from the committee members on the Conflict of Interest

Statement?

[No response.]

Committee Discussion

DR. KIEBURTZ: I just want to sort of housekeepingwise deal with three things that were brought up yesterday. One is receiving copies of the checklists. Each of the members of the committee should have gotten that. If you don't, let us know and we will distribute it. We won't discuss that right now, but I just want to make sure you have it.

Then, there were two other questions. I believe Dr. Goldstein brought up both of them. One was about integrating or summing across infections. Folks from Biogen Idec, there was a slide that was proposed to look at that, I think it's 16-91.

DR. PANZARA: Thank you, Mr. Chairman. It is Slide 16-91.

[Slide.]

This is a summary slide of the data we did share with you yesterday except that now it's all, as requested, compiled into a single slide. This

is the placebo-controlled experience in the middle portion, but on the far right side of the slide, in the shaded portion, is the cumulative experience. It includes all open label, as well as placebo-controlled.

Focusing on the top line was the overall infection rate. Again, it was 74 percent in each group, and the cumulative exposure, there was additional exposure, the incidence is 65.6 percent, herpes infections 6.1 versus 7.2. Again I shared that with you yesterday, the cumulative is 6.1.

Now, the way this is set up is you have the overall infections, the herpes and the serious infections are a subset of that overall infection, and those rates are given. Again, serious infections were balanced and remained a similar rate in the extended experience.

Then, underneath serious infections, you have the subsets of serious herpes infections and opportunistic infections, and then under opportunistic infections, you have the subset of patients who developed PML.

So, that is how the data is rolled up into our overall serious and overall infection rates, and I call your attention to the bottom of the slide where we have done the same for malignancies at 1.3 percent on placebo versus 0.7 percent on natalizumab, with a cumulative incidence of 0.7 percent, and the deaths. Those are the same deaths that I outlined for you in detail yesterday.

DR. KIEBURTZ: Thank you.

Another question was on the prevalence, the numbers, the treatment discontinuations in various randomized studies of interventions for MS. I can't remember who actually asked that question. I am sure the record will tell us. But Dr. Walton has prepared some information to give us sort of the scope of that.

DR. WALTON: We have a slide also. Sohail has the table that could be passed out for the committee, but Dr. Goldstein had asked for what the treatment discontinuations were in various prior experience.

[Slide.]

That slide and table that is going around gives some of our prior experience over the course of more than the past 10 years in studies from a variety of different sponsors in multiple sclerosis.

Obviously, longer studies tended to have somewhat larger treatment discontinuations, just as kept occurring during the course of this study.

The lower part of the table, there are both the treatment discontinuations that were designated as being related to an adverse event and also those that were designated as listed just patient decision or patient choice, which may be relevant to the question that Dr. Goldstein was asking, which was I think trying to infer what treatment discontinuation in clinical practice might be, so patient choice might fall into that, as well.

The bottom box listed two natalizumab studies that we heard about here yesterday.

DR. KIEBURTZ: Thank you. So, I think that sort of cleans up some of the housekeeping

from yesterday.

Does anyone think that they are going to be drafting an additional question to the questions that were already proposed by the FDA? Just so I know. You don't have to tell what it is.

DR. GOLDSTEIN: We may be able to integrate it in part of the other discussion, but it gets to the issue of what patients and physicians should be told about not only what we know, but what we don't know as part of that informed consent process. We may be able to integrate that into part of the other discussions.

DR. KIEBURTZ: Let's see how that goes.

Dr. McArthur?

DR. McARTHUR: Do you want to know what the question is now, or just that I am composing it?

DR. KIEBURTZ: Just that you are composing it. It sounds like you are. Just so I can plan, just because we have quite a list of questions before us.

Before we address the questions, are there

any additional clarifications from the sponsor or the FDA that anyone wishes to ask at this point? Dr. McArthur or Ms. Sitcov, either way.

MS. SITCOV: Perhaps this question is better asked of the FDA. When Dr. Richert spoke yesterday, one of the things that struck me is that the current drugs that have been available for MS don't really have a fatality rate connected to them, or morbidity, I guess, is how it would be termed, but the 1 in 1,000 figure that exists now for this drug, how, when you compare drugs for other autoimmune diseases, such as rheumatoid arthritis, or Crohn's disease, or lupus, where does 1 in 1,000 come out in comparison with those kinds of drugs, because for the current MS drugs, we don't see those kinds of numbers.

DR. WALTON: I would say for some of the more recent products for things like rheumatoid arthritis, which have been the TNF antagonist products, those do have serious side effect risks associated with them.

Probably amongst the most prominent are

two categories. One is infectious risk and one is concerns about malignancy. On the malignancy side, it is very difficult to figure out what the drug associated risk is, because there is a strong impression that malignancies are higher in the rheumatoid arthritis population than in the general population, but it is very difficult to figure out exactly what that background rate is because most of the rheumatoid arthritis patients are on other forms of immunosuppressive drugs, so distinguishing between the true background rate and their drug associated rate for the other drugs is confusing.

So, consequently, the data we have on malignancy rates in people being treated with the TNF antagonists becomes difficult to interpret. We do believe that there is some drug associated increased risk, and those products have warnings related to that, but we don't have a good quantitative number for that.

With regards to infectious disease risks, again, we have some good numbers that I do not recall offhand, that are certainly higher than 1 in

1,000 for bacterial type infections, and those are in the label, and those were things that we saw in controlled clinical studies and can have a good estimate for.

Of course, for those, for bacterial infections, we have antibiotics that can treat those if picked up early, so a good surveillance of patients can help ameliorate those risks for the sake of prompt treatment.

There are less common infections like tuberculosis that we have seen with those products. Again, we have an approach that we have confidence decreases those risks - the testing for TB prior to initiating the TNF blockers, and again surveillance to institute treatment, to be suspicious for the development of TB and institute treatment.

They are a little bit different in terms of the nature of the risk.

DR. KIEBURTZ: Let me just make sure. I don't want to start edging in to discussing the questions yet. This is getting clarifications of material that was presented yesterday. That is

what we are doing right now.

Dr. McArthur.

DR. McARTHUR: My question is for the sponsor, and it relates to the issue of certainty of diagnosis and identifying patients with multiple sclerosis who might be most likely to respond to the drug in question.

So, has an analysis been done or are you able to present an analysis of treatment response in terms of relapse frequency or changes in MRI images for patients who entered the trials 1801, 1802, with contrast-enhancing lesions? So, is there a subgroup analysis of just that patients?

DR. SANDROCK: We have done that, stratified patients based on the presence or absence of enhancing lesions at baseline. Could I have the slide that shows that, the relapse rate ratio, please? Yes. Could I have Slide 422.

[Slide.]

This is the annualized rate ratio where the vertical line is a ratio of 1 and points to the left of 1, indicate a treatment effect in favor of

natalizumab.

Patients with zero enhancing lesions and at least 1 enhancing lesion are shown here. The confidence intervals do overlap in both groups. You see a substantial treatment effect. Even the patients with less than 1, or even patients without lesions have a rate ratio that looks like it's a little left of 0.5, indicating a greater than 50 percent decrease in the frequency of relapses.

Does that answer your question?

DR. MCARTHUR: Thank you. Just remind us, if you can, what proportion of patients at baseline had contrast-enhancing lesions?

DR. SANDROCK: It's about 49 percent, as I recall, in this trial.

DR. KIEBURTZ: Dr. Sandrock, while you are up there, can I ask you a couple of other questions.

The actual cumulative probability of relapse by two years in 1801?

DR. SANDROCK: Yes. It's from my core presentation, the risk of relapse, the Kaplan-Meier

plots.

DR. KIEBURTZ: The numbers are called out at Year 1.

DR. SANDROCK: The reason for that is that that was a prespecified secondary endpoint, the proportion of relapse-free patients. It was not a prespecified endpoint at either time. I restricted my talk to all the prespecified primary and secondary endpoints.

Could I have Slides 24, please.

[Slide.]

I don't know if the statisticians could give us the actual numbers, but extrapolating from the curve, it looks like about 60 percent of patients had a relapse in the placebo group compared to about 30 percent in the natalizumab group, something like that.

DR. KIEBURTZ: So, for the context of our future discussion, let's use those as round numbers, 30 and 60 percent of two years risk of relapse in 1801.

DR. SANDROCK: It looks like it's about

right.

DR. KIEBURTZ: That's fine. Can I ask you another question? The rate ratios are hazard ratios for relapse and for progression of disability by EDSS stage. You showed us that yesterday, the subgroup analysis.

Could you just show us those again for both endpoints?

DR. SANDROCK: Sure. Could we have I guess it would be display 2-9 and 2-10 from the briefing document.

DR. KIEBURTZ: To the other committee members who have questions, I realize I have jumped the agenda, but I figured since Dr. Sandrock was there, I would just--

[Slide.]

DR. SANDROCK: So, this is display 2-9 in your brief document. The third segment are the EDSS scores at baseline - zero to 1, 2 to 2.5, 3 to 3.5, and greater than or equal to 4, and the relapse rate ratios are shown there.

DR. KIEBURTZ: Could I just clarify, the numbers in parentheses following the greater than stage 4, 37 and 79, so there were maybe 120 subjects in the trial who had an EDSS score of 4 or higher.

DR. SANDROCK: Yes, that's exactly right.

DR. KIEBURTZ: Thank you.

DR. SANDROCK: The next slide 247 shows the hazard ratio.

[Slide.]

This is the hazard ratio based on the cumulative probability of progressing by two steps on the EDSS scale, again, the same divisions on EDSS, and you can see the hazard ratios there.

DR. KIEBURTZ: Thank you.

Go ahead, Dr. McArthur.

DR. MCARTHUR: Would that particular slide, which is 217, it looks like individuals, you have a relatively small number of T2 lesions. There is no treatment benefit.

DR. SANDROCK: Well, it's a very small subgroup, 15 patients in the placebo group, 29 in

the natalizumab group. The confidence intervals go virtually across the entire screen.

On this relatively insensitive endpoint, the number of events must have been very small, so it would be hard to conclude one way or the other I would think.

DR. MCARTHUR: I think that the point I am trying to make is again how do we identify which patients should or should not receive this agent.

DR. SANDROCK: I understand.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I had a point of clarification. I vaguely recall--and I wanted to check whether this was right--that there was an adverse event discussed yesterday in a child?

DR. SANDROCK: Yes.

DR. M. HUGHES: The question then is how much pediatric data do we have, and is pediatric use being considered as part of the RiskMAP.

DR. SANDROCK: The child you are referring to was a single patient IND. This was a little girl about 1 1/2 years old, who had a fulminant

inflammatory disease of the white matter, that was later biopsied and found to be consistent with multiple sclerosis.

She has been tried on interferon, high-dose interferon, cytotoxic agents, and she was declining, and we were asked to provide natalizumab on a compassionate use basis. We did so. She seemed to initially respond, and then she seemed to worsen again. The natalizumab was discontinued, and she eventually expired.

Other than that, we have not done a formal study of natalizumab in pediatric MS patients, and we are not seeking an indication for pediatric MS.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I have a question for the FDA, I am not sure which person. Not being an MS expert, it is important for me to understand, for MS patients, other potential therapies, and we have heard about a lot of them, and you have given us some numbers this morning on discontinuation rates.

There is one, though, that is mentioned, that does have some toxicity, and I just want to

understand a little bit more from the FDA's perspective something about I guess it's Novantrone or mitoxantrone that has the cardiac toxicity.

What is that about, the risk of toxicity, and does that have a specific labeling, and how that was dealt with? I know that's a complicated question. It just helps me to put into perspective other MS drugs that have been I assume approved with possible other kinds of toxicities other than infection.

DR. KATZ: Novantrone was approved for a different form of MS, for progressive forms of MS, and not relapsing-remitting, and it had been known, based on its prior use in the form of cancer, that it had a cumulative cardiac toxicity, cardiomyopathy basically, although it has recently been determined that cases of heart failure can occur even if there are one or several doses, and the original labeling said that you shouldn't get over, I think it was--I forget--140 or 120 mg/M-squared cumulative dose, and patients were supposed to have been followed.

After they achieved I think 100 initially, they were supposed to have cardiac evaluation, but that labeling has now been changed to require, essentially require cardiac monitoring prior to each dose.

When it was approved, it was approved with a requirement for the sponsor to follow a certain number of patients, several hundred patients, I think, to monitor to see actually what the incidence of this cardiomyopathy was in MS patients.

Then, it was also approved with a requirement for the sponsor to do a study to look at, in a real world setting, whether or not these studies were actually being done according to labeling. At least preliminary evidence from that study suggested that the protocol for the cardiac monitoring wasn't really being followed terribly well, although we didn't have very much data at this point, because it takes time for patients to get to that cumulative dose, but again the labeling has been changed to ask for cardiac monitoring

before each dose, because cardiomyopathy can occur with far less than 120 mg/M-squared.

DR. SACCO: I guess what I am trying to understand is it wasn't maybe a RiskMAP, but the sponsor proposed certain things that would be done, and from what you are implying, some things were done and some things weren't done.

I just wanted then to follow up with when there is toxicity in a drug, and there is proposed labeling as well as plans to follow up, how compliant, how accurate, how responsive are both the sponsor and the FDA in interpreting and acting on that follow-up data?

DR. KATZ: Well, I think it depends on the nature of the agreements. If I recall, in the Novantrone case, there wasn't a mandatory enrollment of the sort that the sponsor is proposing now here, so that not every patient who was prescribed Novantrone was enrolled into a registry, followed forward prospectively. It was handled quite differently.

You are asking how likely is such a

registry to be successful, is that the question?

DR. SACCO: Well, let's stick to just Novantrone, and you just implied that there were some cardiac echoes done, but you implied that the preliminary--in other words, I didn't have a sense from you that that was a robust interaction between the FDA and the sponsor in the monitoring of the cardiotoxicity with this drug, unless I misinterpreted what you said.

DR. KATZ: It was quite a robust interaction in terms of agreeing to what sorts of monitoring ought to be done, or what sort of labeling would be required. Clearly, we had a great deal of negotiations about the labeling.

DR. SACCO: Before, but then the follow-up.

DR. KATZ: Again, there were two studies, as I recall, required for Novantrone. One is for the sponsors to actually enroll, I think it was several hundred patients, and monitor, and another study was to just look at sort of the real world and what actually was happening.

We got periodic updates on both of these studies, so there was quite a--I would say, to use your word--robust interaction in terms of follow-up, but again, in terms of the total use of the product once it was approved for progressive MS, there was not the sort of required registration of every single patient before the drug was released, but, no, we got, and continue to get, periodic updates on both of these studies.

But again, at least initially, when the toxicity was considered to have been exclusively related to a cumulative effect, with very early exposure, there was very little data, because there was no requirement to do the testing until much later.

DR. KIEBURTZ: Let me just remind the committee--and then we are going to have Dr. Temple speak--that I really want to focus right now on clarifications of things that were presented yesterday, and we are getting ahead of ourselves, because a lot of these things we are talking about, we are going to come back to, and I really don't

want to do it twice today.

Dr. Temple.

DR. TEMPLE: I just want to note a complexity. Novantrone is an anticancer drug. It's available for the treatment of cancer. When you get a novel use, it's not so easy to put a special treatment regimen, because people can readily avoid it and just use the other drug. We have encountered that in other settings.

I guess the other thing I would say is we are becoming, and have been becoming, as is indicated in some guidance we have written, increasingly conscious of the need to look at the impact of the risk management programs that we have, and you saw some of that here.

A perfectly good question is what are you going to do now that you are discovering that people aren't doing that, and there are things you can do. You can give patient labeling. Most cancer drugs don't have patient labeling, but there could be a so-called "Med Guide" made available, and we need to think about all of those things, and

that is what we do.

But I would say there is an increased level of consciousness of the need to not just put something in place, but to see how it's going, and the guidance we put out makes that point.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: One of the questions that I had asked yesterday that must have fallen off your list was I asked for the numbers needed to treat data, and I asked for three things really.

It was numbers needed to treat to prevent one relapse over two years, to prevent progression of disability, and to prevent one of the major clinical endpoints, and I asked for it in two ways, one based on the control data from the 1801 trial, and then if you presumed a one-third response rate in the placebo group in that trial, since there was no head-to-head comparisons and we are told that there should be about a third response rate in the placebo group, what those numbers would work out to, and presumably also with the confidence intervals around those.

DR. KIEBURTZ: The sponsor may have an answer, but my back of the envelope number needed to treat two years, that is why the 30 versus 60 gives you a number needed to treat of about 3, and EDSS progression number needed to treat is about 8.

DR. GOLDSTEIN: From the numbers that we had from the FDA table on page 2 of their presentation is a slide, Slide 5. Just looking at the 1801 efficacy analysis, looking at the numbers of patients reaching a sustained disability progression, it actually works out to--if you go through all the math, it works out to a 1.2 percent absolute reduction that is not statistically significant assuming a one-third response rate in the controls, but I am not a statistician, you know, I did this on my calculator. That is why I want somebody who does know how to do these numbers to do them.

DR. KIEBURTZ: Dr. Sandrock.

DR. SANDROCK: Could I have Slide 16-79, please.

[Slide.]

Our statisticians did this calculation last night, and here are numbers. This is based on the 1801 monotherapy trial. Based on the annualized relapse rate, I put the actual annualized rates from the two treatment groups, the relative treatment effect, the absolute difference, and NNT is 1, so 1 patient is needed to be treated to prevent one relapse.

If you look at the proportion of patients relapsing, the NNT is 4, so 4 patients needed to be treated to prevent 1 patient from relapsing.

Based on the proportion progression, our calculations indicate 9 patients need to be treated to prevent 1 patient from progressing on the EDSS scale.

DR. GOLDSTEIN: And if you assume a response rate in the control group, because the control group here is placebo, but we are not comparing this to placebo anymore, we active treatments that work, that reduce the rates about a third.

DR. SANDROCK: So, we did that by

looking--could I have Slide 16-80, please.

[Slide.]

So, this now looks at the added benefit of natalizumab compared to patients who are only on Avonex from the 1802 trial. Again, the absolute numbers are listed here.

So, 2 patients needed to be treated in order to get a benefit of natalizumab compared to just being treated with interferon, 5 need to be treated to prevent 1 patient from relapsing compared to just treating with interferon, one of the current available therapies, and 17 need to be treated to prevent 1 patient from relapsing compared to just staying on the interferon.

DR. KIEBURTZ: I don't think we want to speculate too much about--these are the data from the two trials that are at hand, extrapolating outside of them would be difficult.

Dr. Porter.

DR. PORTER: You are going to discuss this checklist later in detail?

DR. KIEBURTZ: Yes.

DR. PORTER: I will pass then.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: Again, this is a question for the company, and I suspect there is a rather simple answer for this, but the censoring data, let's just look in 1801. By week 108, was 9 percent in the placebo and a little over 7 percent in the Tysabri.

Then, when you talk about the total number of patients that were censored, it is listed as 73 and 83 percent. I suspect there is a very simple answer.

DR. SANDROCK: On the EDDS scale, two years is the bare minimum required to show enough evidence to show power. If patients haven't progressed by the end of the two years, they are censored. In every single MS trial that has ever been done, the vast majority of patients do not progress by two steps, sustained for three to six months.

So, in every other MS trial that has looked at disability progression, the majority of patients don't progress, and therefore, they are

censored by the Kaplan-Meier methodology.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Many of the anti-immune drugs that are currently available were mentioned yesterday - azathioprine, methotrexate, Cytosan, CellCept, I don't remember cyclosporine being mentioned.

Do we know anything about, just in general, what is the malignancy rate and the serious infection rate for these drugs across the board, or can that information be made available sometime during the day, so that we could compare what we are talking about to these other drugs that were mentioned as possible alternatives to using Tysabri?

DR. WALTON: I think it would be very difficult for the sake that those products have not been approved for use in multiple sclerosis, so we don't have good studies, and data on them from other uses would include some very different ways of using the drugs, so I would be very reluctant to extrapolate those adverse event rates to use in

multiple sclerosis in whatever physicians are using them off label.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: From the practical standpoint, however,, since MS patients are using those drugs off label, it would be useful to be able to compare what few numbers we do have, accurate or not, compared to what is known about Tysabri, number one. Number two, going back to Dr. Sacco's question, what is the number, do we know that the number of AML that has been diagnosed with the use of mitoxantrone in the setting of MS treatment?

DR. KATZ: As far as leukemia, it is a couple of patients, I think, in MS. There are probably people here who can better speak to that, but there is one or two cases I think reported, but I don't recall exactly. I suppose we can try and get that information.

DR. JUNG: Based upon how many numbers treated.

DR. KIEBURTZ: Dr. Rudick, can you speak to that?

DR. RUDICK: I don't have the exact numbers in front of me, but at the European MS meeting, there was a report of some 18 cases or so from France with AML, who used mitoxantrone.

Anecdotally, I had a patient that just went in the hospital with acute leukemia from mitoxantrone, so I don't know that we have the numbers, but it is clearly more than one or two cases.

DR. KIEBURTZ: As usual, we want evidence where we don't necessarily have it, but anything we could accumulate by this afternoon, I suppose, about any evidence or reports regard AML might be of use.

Dr. Temple.

DR. TEMPLE: Just for something like mitoxantrone, the cardiac problems depend on how long you use it, but what it does is very familiar from daunorubicin and doxorubicin. It is part of cancer chemotherapy. It is unquestionably lethal if you keep going in the face of deteriorating cardiac function, so it is very hard to put a

comparable number on it, because it is dose related and all that.

DR. KIEBURTZ: I have a question for Dr. Bozic about yesterday's presentation. Slide 94, about the registry, the last bullet. I just want to make sure I understood that correctly.

So, it is proposed in the registry that all spontaneously reported events would be collected as part of the registry.

DR. BOZIC: That would be standard practice in safety surveillance that we collect all adverse events, so I wanted to make it explicit that, of course, in this mandatory registry, we would collect all adverse events and include those in the analyses.

DR. KIEBURTZ: And adverse events as defined in standard TCP, worsening of pre-existing conditions.

DR. BOZIC: So, any report that a physician would call in to us, or a patient would call in to us, either spontaneously or in the course of, for example, a contact that we make with

the physician.

Let me give you an example. Every six months we are going to be contacting physicians to tell us about whether any of their patients has had PML or another serious opportunistic infection, or whether the patient has died, or whether they discontinued Tysabri.

In the course of some of those contacts, we may get additional information on other adverse events. So, of course, I just wanted to make explicit that we will collect all adverse events.

DR. KIEBURTZ: Let me put a finer point on my question. So, the bullet before it says physicians are queried on every patient every six months.

DR. BOZIC: Yes.

DR. KIEBURTZ: So, they are going to be asked about these things.

DR. BOZIC: Yes.

DR. KIEBURTZ: Are they going to be asked to report at that time all adverse events?

DR. BOZIC: No. No, they won't be asked

to report all adverse events. The question will be specifically targeted around the occurrence of PML, any other serious opportunistic infection, any death, and any discontinuation, so it is a very targeted tracking system to evaluate further the events of high interest, the PML and the other opportunistic infections.

DR. KIEBURTZ: So, that bullet that says, "Collect all spontaneously reported adverse events," means if somebody calls you, you will keep track of it.

DR. BOZIC: Absolutely, and that is standard practice in post-marketing safety.

DR. KIEBURTZ: I got it. Slide 97, the frequency of evaluation in the proposed observational cohort study?

DR. BOZIC: Yes. In that study, we will be contacting physicians every six months to report all serious adverse events, as well as all concomitant immunomodulatory or immunosuppressant therapies, and any discontinuations, as well.

So, in that study, in addition to

collecting the PML, the serious opportunistic infections, and deaths and discontinuations, we will collect all other serious adverse events, as well.

DR. KIEBURTZ: You use the same verb there, thought, "collect," but in this, you are asking the physicians to make a--

DR. BOZIC: We are actively soliciting.

DR. KIEBURTZ: Actively looking for all SAs.

DR. BOZIC: Yes, exactly, much like in a clinical trial, for example.

DR. KIEBURTZ: Sorry to come back to this, but you said you will contact the physicians for this information. What is the proposed frequency with which the physicians will have an in-person evaluation of the patient in order to fulfill the obligations of the cohort study?

DR. BOZIC: So, because this is an observational study, the frequency of contact between the physician and the patient will be according to whatever the labeling says. Okay?

Now, part of the purpose of both this study and the Tysabri Registry is that this six-month contact with the doctor is intended to be a prompt for the physician to, you know, ascertain the status of the patient, because this is a study, it's a non-interventional study, so the frequencies of contact between the doctor and the patient would be according to whatever the labeling would say on that matter.

DR. KIEBURTZ: So, let me just restate that another way.

The cohort isn't proposing any more frequent contact than what is mandated by the label.

DR. BOZIC: Exactly.

DR. KIEBURTZ: Okay. Thank you.

Dr. Sejvar.

DR. SEJVAR: Just a quick question for the sponsor just for my clarification.

There really hasn't been a lot of pharmacokinetic and pharmacodynamic information presented to us, but had basically hematopoietic

factors been looked at long term, and are there plans to continue those assessments?

DR. SANDROCK: We did look at hematopoietic factors in the Phase III trial for two years. There is a transient slight decrease in the hemoglobin. It does seem to go back to normal.

In terms of, I don't know, when you said "hematopoietic," whether you meant immune cells, as well. Yes, we are planning to do an immune function study, vaccination study, for example.

DR. KIEBURTZ: Dr. Sacco, then, Dr. DeKosky.

DR. DeKOSKY: Back to I think Dr. Bozic regarding the risk management plan, on Slide 96, I guess, because I have asked the FDA a little bit, I ask the company a little bit, the last bullet, you say, "Ongoing assessment of benefit-risk," and I just want to get a better handle about what kind of ongoing assessment and what kind of possibly qualitative or quantitative rules you would use to make any alterations in decisions?

DR. BOZIC: I believe the question you are

asking is in the Tysabri Registry, we say that we will assess the benefit-risk profile of Tysabri in an ongoing fashion. What we mean by that is because we will have a complete denominator of all Tysabri-treated patients and complete ascertainment of every PML case, we can track the rate over time of the event, the PML event.

In addition, because we will know all relevant information about that case, we will know the outcome of the case, and we are going to carefully investigate all aspects of the case, looking for potential risk factors, for example, underlying comorbidities or concomitant therapies that might have contributed to the development of the case.

So, that is what I mean by an "ongoing assessment of benefit-risk." I just want to point out this is very, very different from the usual post-marketing setting of most drugs, where we generally don't know completely how many people have been exposed. We usually don't know completely how many cases have occurred due to

under-reporting. So, we have severe limitations typically in the post-marketing setting.

So, this registry is dramatically different from what usually happens when a drug gets introduced in the marketplace, because we will know all prescribers and every single patient and every single case.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: This may be a question for Dr. Sandrock as a follow-up to Dr. Sejvar's question.

The discontinuation of a drug to go into a trial with or into treatment with Tysabri was a two-week plan, I think, and it was based on the PK.

So, the PK, I presume is purely in terms of clearance of the medication or detectable levels of the medication, and my question was about other effects, not necessarily hematopoietic, but other systemic effects that probably would outlast the PK change and whether that is accounted for in those two weeks, as well, or whether there is reason to wait longer.

DR. SANDROCK: Actually, it is based on the PK and the pharmacodynamic effect, so we can measure biological responses to interferon by looking at interferon-inducible genes or their gene products, and some of those inducible responses can persist for approximately one week, so that is why we recommended the two weeks.

DR. KIEBURTZ: Dr. McArthur.

DR. MCARTHUR: Dr. Sandrock, sorry to have you jump up and down, but could you go back over the thinking about the collection of serum specimens? In some of the cases that were presented yesterday, serum JCV-PCR did become positive before the onset of PML symptoms.

I realize that you don't have all of the sensitivity, specificity, performance characteristics pinned down, but why not attempt to collect serial serum samples as part of the RiskMAP program?

DR. SANDROCK: I may ask Dr. Panzara to supplement my answer, but the bottom line is that we have extensive data from our safety evaluation.

We felt that the sensitivity and the positive predictive value are so low that we could not recommend widespread use.

We chose instead to study this in our re-dosing trial to understand more about how often you get positive. Since we don't understand the meaningfulness of a positive result, since people who weren't even on Tysabri got positive responses, and we have seen it in HIV and other places where people become positive, and they don't get PML, we wondered how disruptive this would be in the practice to have a positive results, what is the meaningfulness of that.

So, if Dr. Clifford or Dr. Panzara would like to come up and comment further, because we did develop these plans based on expertise from people like Dr. Clifford.

DR. KIEBURTZ: So, the speaker is Dr. David Clifford, who was introduced yesterday in the sponsor's presentation.

DR. CLIFFORD: Right. I am obviously a member of the Independent Adjudication Committee

that was trying to look at the experience of the population exposed to natalizumab and the relation of that exposure to possible markers for PML or the risk of PML.

Our main obligation was really to seek out cases that we could definitely identify as PML cases, and as we reported last week in the New England Journal, there were no cases with really quite an extensive effort to identify them both through many CSF analyses and MR analysis, and careful review of the clinical evaluations of the patients.

We know that this JC virus is present in normal people, in a majority probably of normal adults, and that, in fact, there is replication and shedding of this virus certainly in the urine of most normal adults at as much as 30 percent of the time.

We are also aware that it is present in the serum, the plasma specimens when carefully measured. Frankly, we decided ahead of time that this was a measure that we couldn't factor into

diagnosis of PML at all based on the experience of many cases followed over time with a high risk of PML, who have circulating plasma JC and never develop the disease.

Frankly, I was quite surprised that there were so few cases of circulating JC virus in the population surveyed, and the fact that with the commercial survey that we were able to do, the large, more than 2,000 samples, that a majority of those had circulating virus in those never exposed to natalizumab, made us believe that the signal was, at this point, quite a weak signal, and that we scientifically could not interpret it.

It would require a very large study to probe that more deeply, to have a scientific basis to say that this was a risk factor for future development of PML.

I think it remains a fascinating problem, and I do hope that I can work with the company and probing further any other ways that we could identify risk from that circulating virus, or their rearrangements or other things that could predict

it, but at this point, really, I think the interpretation of that is so difficult that we really wouldn't know what to tell a patient in whom we found positive circulating JC DNA.

DR. McARTHUR: Just as a follow-up, I accept what you say, but I guess my question or point was why not collect a serum specimen from individuals who would go on to receive Tysabri even if you are not using those results individually in those patients to decide anything, because I think I agree with you, you can't tell anybody anything sensible at this stage, but if there were a crop of PML cases down the road, those banked specimens--

DR. CLIFFORD: Samples banks would be a very rational thing to be able to look at to identify risk patterns if they exist.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Since we are talking about blood, something else came to mind that I want to get clarification on.

We heard yesterday about hypersensitivity reactions, some of them being serious, some of them

not, but up to possibly 10 percent. In the risk management plan and in some of this blood collection, I didn't see much mention of how that falls in, whether you collect blood for checking for antibodies and whether antibody positivity affects continued use of the medication.

Maybe I missed it, but if somebody can just clarify that.

DR. KIEBURTZ: Can I change that question around a little for you? Do you currently plan to be screening for neutralizing antibodies as part of the registry or the cohort?

DR. SANDROCK: I just wanted to clarify one thing, the rate of hypersensitivity reactions. Could I have the slide on hypersensitivity reactions, please, Slide 8-12, please.

[Slide.]

Actually, the incidence of hypersensitivity reactions in the 1801 monotherapy trial was 4 percent. So, there were 25 reactions, 25 patients with 27 hypersensitivity reactions, so a couple of patients had them twice.

Fifteen reactions occurred on the second infusion, and the incidence of serious hypersensitivity reactions was 1.3 percent.

So, this is the rate in the monotherapy situation. In the combination trial, it was lower, but we think this is the rate that is applicable since we believe Tysabri should be used as monotherapy.

DR. PANZARA: The only thing I would add to that is that the rate of 0.8 percent you saw yesterday was the placebo-controlled experience, so was the overall experience, hence, the 1.3 versus the 0.8, and it was actually very similar to the anaphylactic, anaphylactoid rate that you see on the bottom of the slide.

I would also like to say that there will be a commercial test available for the testing of the neutralizing antibodies, and it is recommended that anybody in which there is a suspicion of diminished efficacy or, as was described yesterday by FDA, the occurrence of certain adverse events, such as flushing and other things that would make

physicians suspicious that person may have neutralizing antibodies, we would recommend testing, and if the test is positive, the patient should not receive natalizumab.

DR. KIEBURTZ: Thank you. That answers my question.

Well, hopefully, stretching helps before running, because that's what we did for the last hour, so I would like to turn our attention to the questions, and thank you to the sponsor for being responsive to our questions.

Response to FDA Questions and Committee Discussion

DR. KIEBURTZ: The first two questions are has Biogen demonstrated efficacy on the reduced frequency of relapses through two years and fulfilled the commitment made under the Accelerate Approval conditions to verify the sustained clinical benefit.

Is there anyone who feels that the answer to this is no?

[No response.]

DR. KIEBURTZ: So, everyone unanimously

agree that they have met that condition, they have fulfilled the commitment? Okay.

Question 2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?

Any discussion about that?

DR. RICAURTE: I have a question in that regard. This is to the Agency.

There was a comment made about--this has to do with progression to disability--that between the screening exam and the enrollment, there had been variability in terms of the score obtained on the EDSS and how that complicated matters.

I guess the question is: How did that variability between screening and enrollment compare relative to the treatment of that? I am just trying to get a sense of how much is natural variability, how much is the treatment, how does that compare, and why, just to expand on the comments that were made in the written statements here on the Agency's analysis.

DR. WALTON: Okay, let's see. Some

answers and not exactly necessarily in the way that you have asked them.

The screening and the official baseline exam, as I understand, were done by the treatment and the evaluating physicians, they were done by different physicians, so that is a portion of the variability.

Another portion of it is we know from all of the multiple sclerosis studies that we have done, that there is a variability from time to time, from evaluation to evaluation, even with the same patient and the same physician in the EDSS.

That variability is a portion of the assessment that went into the determination that we have to have a full point, a full 1 point EDSS change to, and sustained over some number of months in order to be able to confidently regarded as a meaningful, reliably assessed change.

So, that variability is something we see in every study. In terms of the impact, if one uses the screening exam instead of the baseline, you have some patients who shifted down between the

two, and therefore are a new progression that were not previously deemed a progression in a few patients that shifted up, and they lose their designation as a progresser.

It does make a little bit of difference in the exact numbers, you know, for each group, the exact percentage who are deemed progressers. It is a little bit larger fraction of exactly which patients get deemed progressers, but the net effect is that the treatment effect remains, and the precise, the point estimate shifts slightly one way or the other in each arm, but there still remains a clear-cut treatment effect between the groups.

Have I answered?

DR. RICAURTE: Yes. The second thing would be just I don't use this scale, I am not familiar with it, but just to get a sense of clinically, what does this mean, a change in 1 point, 1.5 points. I am looking at the scale, but it is kind of hard to get a sense.

So, relative to the variability that one can see depending on the examiner, depending on

time, how robust is this treatment effect, and what does it translate into clinically?

DR. WALTON: I think I will break your question into two parts. One is how robust is the treatment effect. Our analyses convince us that the treatment effect is robust in the sense of various ways of looking at it, some of which have been shared with you in these documents, and other ways that we have tried to tease apart what is occurring, that are just too arcane to try and fill into the briefing document. We do believe that the treatment effect is robust to analysis.

The other part of your question, though, is I think what is the meaning of this change, and for that, the EDSS scale is not a linear scale in the sense of every interval along it has the same meaning to the patient. At the very lowest end of it, a 1-point change is really translated more as a reliably determined change in clinical signs that one can reliably and reproducibly determine on the patient. That is at the very lowest end of it.

As you move up, it really does become a

disability or impairment scale that will take into account upper limb function, real impairments that are meaningful, perceptible to the patients in upper limb function, as well as lower limb function, as well as a bladder function.

As you get into sort of the middle range and higher, the scale really shifts into some significant amounts of impairment in ambulatory ability and becomes very big changes in that, but experience has seen that for this scale, it needs to be that large a change in steps in order to be confident that it is reliably a real change in the patient's condition, and not part of their day-to-day, week-to-week variability of function related to a constant disease state.

Does that help?

DR. KIEBURTZ: I would just throw in there, I am not sure, we could probably spend the better part of today and tomorrow arguing about a clinical equivalent of EDSS scale, and not to close it off, but I think the general consensus is that this definition of disability progression is

acceptable, if not universally acknowledged.

So, back to Question 2. Does anyone feel that Biogen has failed to demonstrate efficacy on reduced accumulation of physical disability as defined in the protocol?

[No response.]

DR. KIEBURTZ: Then, we are all in unanimous agreement that they have. I believe there is 12 voting members, so I would say, we didn't take a formal vote, but it's unanimous.

DR. KATZ: We don't need a formal vote on this question.

DR. KIEBURTZ: Thank you.

DR. WALTON: There is one question for which we do want a formal vote, but the others you need not impose that.

DR. KIEBURTZ: Just for the context, just bear in mind, Dr. Sandrock put up a slide with numbers needed to treat, so rather than 60-30, the percentages of people who had a relapse by two years was 54 percent and 28 percent, so roughly speaking, about half the people in placebo did not

have a relapse, and about 75 percent in the treatment group did not have a relapse.

Roughly, a quarter of the people in placebo had disability progression, I will a third, and half of that did in the treated group. So, these are minority events. Most people didn't have the events. Most people in these studies did not have a relapse and did not have disability progression.

The frequency of relapse is about twice that of disability progression, but still I guess 54 percent is technically a majority, but just to frame up the events.

On to No. 3. Outside of PML, are there safety-related issues associated with the use that you consider to be important considerations in making a risk-benefit assessment including non-infectious disease risks and non-PML infectious disease risks?

So, non-infectious disease risks, those would include the things we have heard about, malignancies, hypersensitivity reactions, and so

forth. There are important other safety-related issues that we should be thinking about.

Dr. Koski.

DR. KOSKI: Well, I think when you look at the numbers of patients relatively in the placebo arm and the Tysabri arm, I don't think that it comes out to be very prominent, at least in these two groups, over the period of time that we looked at, but still think it's a consideration when we are talking about patients that are likely, if this drug is approved, to be on it for really long periods of time, much beyond the two-year period.

So, I think over time, cumulatively, they may be an issue, any anytime you have increased risk of herpes, eventually, you know, I would anticipate that we might see like B-cell lymphomas in the CNS.

DR. KIEBURTZ: So, are you speaking to (b), the non-PML infectious disease risk?

DR. KOSKI: Right.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I guess I would go back to

just the hypersensitivity risk. I mean I think there is some, and I think, to me, it is something that is possibly preventable given the antibody detection.

So, under (a), I guess the question is whether hypersensitivity would fit there or not. There were some that were anaphylactoid, and we saw some of the numbers, but is that important? To me, it is.

DR. KIEBURTZ: I will just voice my opinion on this. I think the development of neutralizing antibodies is probably an important event for two things. One, it certainly seems to be a signal for risk of a hypersensitivity reaction, and also seems to be a strong signal of a population that has decreased benefit.

So, when we start considering risk-benefit ratios, it may be favorable in the non-antibody-positive population, but I think we have seen evidence to make us wonder whether it remains favorable in the antibody-positive population. I believe what we just heard from

sponsor is they would promote, they would suggest or have proposed clinically-based testing for antibodies based on the occurrence of side effects, and not recommending any further treatment in those who are found to be persistently antibody-positive, if I heard that correctly. I see nods, so I think I summarized it accurately.

So, I would say to the Agency I think that is a concern.

Dr. Koski.

DR. KOSKI: I would just point that, you know, currently, in treatment of MS with the interferon products, there is a known rate of positive antibodies that actually evolve most frequently after about a 6-month period.

Currently, there are I think evolving recommendations in the field to handle this, because it is realized that when you have these neutralizing antibodies in a specific or consistent fashion, that the drug is not as effective, and at that point, you either change to one of the other drugs that has less of an incidence of antibody, or

to something like glatiramer.

DR. KIEBURTZ: Unless I have misunderstood things, one slight difference here is it looks like--and maybe Dr. McDermott could, or Hughes--I think the development of antibodies was sort of paradoxically quite early on, because it is associated with hypersensitivity reactions, which occurred early on also, so a little bit different than others is that this seems to be a relatively early phenomenon.

DR. A. HUGHES: One of the difficulties--and the sponsor may be able to talk about this a little bit more--but antibody formation was assessed every 12 weeks, and I believe the median time for anti-natalizumab and antibody formation was 12 weeks, but we are not exactly sure in that interval when the formation is occurring. I do think it is quite early.

DR. KIEBURTZ: Any other questions on Question 3?

Dr. Sejvar.

DR. SEJVAR: I am sorry, I just wanted to

clarify with the sponsor, the apparent decrease in response to the product would also prompt looking at the antibody, as well, right?

DR. SANDROCK: Yes.

DR. KIEBURTZ: I think maybe we can incorporate our recommendations on testing, timing, and triggers when we talk about the risk management plan.

Dr. Jung.

DR. JUNG: Do we have any information about the severity of the anaphylactic reactions which occur? I believe previously, when the drug was marketed, that the feeling was that the anaphylactic or anaphylactoid reactions were relatively mild and treatable with just the use of Benadryl.

DR. PANZARA: So, in the clinical trial setting, in the slide I showed you earlier, we have a total of five patients in monotherapy study who had serious systemic hypersensitivity reactions.

We pre-defined these as any event that was urticaria with associated systemic symptoms, mostly

respiratory symptoms. Out of those five patients, there was no cardiopulmonary compromise in any of those patients. Actually, all of them were treated with Benadryl and corticosteroids. One of them received epinephrine, but not in the setting of a blood pressure abnormality. All maintained oxygenation throughout. All recovered fully.

In the later stage, open-label study, there was one case of anaphylactic shock where the patient did have a lowered blood pressure. Other than that, that is the total numbers we have.

DR. KIEBURTZ: Thank you, Dr. Panzara.

Dr. Couch.

DR. COUCH: Just one comment that is self-evident, but I think should be on the record, and that is, we are dealing with a disease that is very chronic and may have a survival of between 20 and 30 years, even 40 years, so we are trying to extrapolate from 2- to maybe 3-year experience, to something that we have no idea of what it was going to be like in the future.

The 10 years, maybe 15 years of experience

with the interferons has certainly shown that the field changes, and we really just cannot predict what is going to happen 10 or 15 years from now.

DR. KIEBURTZ: I think the data we have largely is confined to 2 and 3 years of follow-up with large numbers of people, and we do not know whether there will be accumulating risk or declining risk with further follow-up, but we are going to make our recommendations based on the observations we have, but your point is well taken.

So, let me summarize. I forgot I am supposed to summarize for the record what we decided on 1, 2, and 3.

So, 1 is that Biogen has demonstrated the efficacy on reduced relapse rate and have fulfilled their commitment for the Accelerate Approval of showing a sustained benefit at 2 years.

No. 2 is that they have demonstrated efficacy on the primary 2-year endpoint, which is reduced accumulation of physical disability.

No. 3 is that our safety issues of concern revolve around the unknown likelihood of non-PML

infectious disease causes, which potentially have a signal in this period of observation, particularly herpetic and serious infections, and secondly, the development of neutralizing antibodies and their possible association with hypersensitivity reactions and decreased efficacy are the safety concerns outside of PML.

Dr. Katz.

DR. KATZ: I think what we meant in this question is whether or not the committee felt that there was anything besides PML that we have seen in the data so far that would preclude approval.

So, I think people should sort of think about it in those terms, and if you think you have the answer to that question, fine, I think we do.

DR. KIEBURTZ: Does anyone feel there is any safety issues aside from PML that would preclude reintroduction to the market? Dr. McArthur.

DR. McARTHUR: I think Dr. Sacco's point is a good one. If regular screening for neutralizing antibodies is incorporated into a

safety plan, that would reduce hypersensitivity reactions or could reduce hypersensitivity reactions, and could reduce exposure to non-responders.

DR. KIEBURTZ: So, that is manageable, not a doesn't preclude.

Dr. DeKosky?

DR. DeKOSKY: Dr. Hughes, I thought I saw a 6 percent rate--I couldn't find it when I looked back in my notes--on the number of subjects with neutralizing antibodies, that showed up at the first 12-week assessment essentially.

Was there an increasing prevalence of antibody as they tracked through their two years of exposure, or if you are going to make them, do you make them early, so that this is or is not a potentially increased risk for long-term administration of the drug?

DR. A. HUGHES: Generally, if you are going to make them, you make them early. I think that 90 percent of patients who became antibody-positive did so in that initial 12-week

interval. Yes, it was a 6 percent persistently antibody-positive incidence, and 4 percent transient positivity. I think we know a lot less about what that means.

DR. DeKOSKY: There was no evidence that they tracked consistently with a percent or two over the two years of the study in increasing numbers.

DR. A. HUGHES: No, there was no evidence of that. I should, though, note again that there were some serious hypersensitivity reactions that occurred further out than would be expected. There was one associated with the 13th infusion, but most did occur in association with the second infusion, as would be expected.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Dr. Hughes? Sorry.

DR. A. HUGHES: I think Dr. Walton wanted me to clarify that not all hypersensitivity reactions were associated with anti-natalizumab antibodies, but all anaphylactic reactions were.

DR. DeKOSKY: My issue had actually more

to do with the risk over time and abatement of clinical response, not so much necessarily the hypersensitivity reaction in terms of approval beyond what we know about what happens with the biological effects of the drug. Thank you.

DR. A. HUGHES: It doesn't seem to be cumulative based on what we know.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Dr. Hughes, the first measurement was at 12 weeks, so we really don't know about early antibody formation and whether one could detect that neutralizing antibody signal at 3 weeks, 4 weeks, 6 weeks, allowing for an early detection of people at higher risk. There seems to be a 10-fold higher risk of hypersensitivity reactions in neutralizing antibody-positive patients.

DR. A. HUGHES: That's right, the first assessment, that's exactly right.

DR. KIEBURTZ: Question 4 is essentially does the committee believe that the risk of PML is limited to patients exposed to a second

immunosuppressive agent, that is, do you think the risk is entirely mitigated by giving the drug as monotherapy. That's how I read that question.

Is there anyone who would say yes to that?

[No response.]

DR. KIEBURTZ: We unanimously answer this one no, that is, the committee believes that there is a treatment-associated risk of PML even when given as monotherapy. None of the observed cases, I mean I think we all understand that none of the observed cases happened in that situation, and it is possible that the co-administration of secondary immunosuppressive agents increases the risk, and it is, in fact, possible that it may only exist in those individuals, but we don't know that yet.

That would be my comment.

Dr. Koski.

DR. KOSKI: I would just go back and point out that the one case in the patient with Crohn's disease was largely on monotherapy. I know that, you know, it was pointed out that we did not have a lymphocyte, a total lymphocyte count on that

particular patient, but he had been off concomitant immunosuppressive therapy for eight months.

DR. KIEBURTZ: Any further discussion on this question? Dr. Hughes.

DR. M. HUGHES: Just a comment for other studies that might be relevant here. It would be interesting to look at the extent of immunosuppression across subjects on monotherapy compared with those on combination therapy.

DR. KIEBURTZ: Do you have a proposed measure of immunosuppression in mind?

DR. M. HUGHES: Not especially, no.

DR. KIEBURTZ: A point well taken. I didn't know if you had an operational plan.

Dr. Sejvar.

DR. SEJVAR: I mean looking specifically at CD counts would be I think very helpful.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: In terms of I think maybe screening patients, one could do some skin testing for common antigens, and I think that is something that we usually use for patients who are going to

undergo immunosuppression, because we really want to already know whether they are in such a condition.

DR. KIEBURTZ: I think these are good points. I am sure we are going to come back to this topic when we define who might be appropriate patients for this treatment.

I would like to move on to Question 5.

I believe this question is--I will ask if I am framing this properly--I believe what we are being asked is do we feel there a study or studies which must be conducted prior to allow remarketing of the agent, that is, do we feel there is something that must be done before we can vote on Question 7.

Dr. Porter.

DR. PORTER: I would just point out that remarketing is not really remarketing in the ordinary sense where the drug is just put into the pharmacy shelves. I mean this is remarketing under a very, very controlled circumstance, so remarketing here has a special meaning.

DR. KIEBURTZ: A point well taken.

Dr. Goldstein.

DR. GOLDSTEIN: Question 5 may be out of order, because I think maybe what we should do is come back to that once we have sort of gone through some of the other questions. I think the way you answer that question depends upon for whom, under what circumstances, and we may need to have that discussion first.

DR. KIEBURTZ: I see your point, but I would say this. I think to frame it like the adverse experience question is if you know right now that you don't think we should return the drug--allow the possibility to return to marketing for anyone until certain studies are done, then, we should know about that now.

Presumably, if you feel that it's not the case, that is only so if we clearly define in whom, for how long, et cetera, and under what circumstances.

Dr. Walton.

DR. WALTON: I think that is exactly

right. The intent of the question was do we have such insufficient information that it's impossible for you to discuss the way the questions, or are you prepared to discuss them.

DR. KIEBURTZ: Are we discussed the later questions? Is anyone opposed?

[No response.]

DR. KIEBURTZ: I will take that as we feel that there are sufficient data to move forward. Of course, all of us think that there will be more data that need to be generated to help refine these questions. That is part of the point of the registry, and that is part of the point of the cohort, and there may be other studies we would suggest in our discussion although that isn't a specific question that has been posed to us.

So, we are willing to move on.

So, the technical answer to Question 5, are there additional data that you recommend to obtain prior to determining whether to return to the marketplace, the answer is no with the caveat that we are going to specify clearly under what

circumstances we think it should be potentially reintroduced.

Is that sufficient discussion? Okay. Well, that's 5 of 11 questions, if anyone is keeping count.

Question 6. There are multiple parts to this question. I think we are getting down to the nub of some of the issues. If we return to commercial distribution, are there specific subsets of relapsing MS populations for whom you would consider use reasonable or, on the contrary, inappropriate?

Then, we have examples, and I don't think we should feel constrained by these particular examples. These were just examples, people who have tried other therapies, people with a certain level of disability needs to be required or have to be below a certain level of disability, whether they have to have tried other treatments, whether they have to have failed other treatments, whether they had to have intolerable side effects from other treatments, whether it should be given with

other treatments.

Now, we have heard from the sponsor, I believe, so (e) is kind of moot in the sense that I believe the proposal is for it to be administered only as monotherapy, and we could consider whether we feel differently, so it is not entirely moot, but we should bear in mind that the sponsor is not proposing at this time that it be co-administered with any other available MS therapy.

There may be other ways of categorizing or characterizing patients who we think are most appropriate for treatment.

Dr. Walton.

DR. WALTON: In spite of the fact that monotherapy is the proposal, I think it would remain useful just to understand whether or not the committee concurs with that or not.

DR. KIEBURTZ: Yes.

DR. TEMPLE: And it has implications for the patient agreement, for example. At present, the patient agreement doesn't say I am not taking anything else, maybe it could.

DR. KIEBURTZ: Understand.

Dr. Koski.

DR. KOSKI: This is actually a question that I am relatively conflicted about, and the reason is as follows. You know, what we are beginning to realize is that the earlier the treatment that you get, the more you prevent disability and presumably the brain atrophy which is the long-term manifestation of the primary progressive or the secondary progressive phase.

So, on the other hand, if you have a patient that is very mild, there is a percentage of them that actually--you know, that you really do not see progress. I will see that that is the minor percentage. On the other hand, if you have a patient who is having a series of attacks, two a year, and has clearly evidence of enhancing lesions on MRI, I think that that is the type of patient that you most likely want to put on monotherapy relatively early in their clinical course.

Additionally, I think the other things that we also talked about is people who were not

able to tolerate some of the ABC drugs and were continuing to have attacks and the same types of enhancing lesions. Again, this is the type of person that you really want to have on it.

DR. KIEBURTZ: I think we can think about defining populations in several ways. One is there are particular characteristics of their disease, that is, do they have relapsing-remitting MS. Another aspect is do they have a certain level of disability, and then there is a separate question about how their drugs have been managed beforehand.

I mean there are several kind of conceptual ways of categorizing people, and I think we should consider many of them, and you discussed two of them.

Dr. DeKosky.

DR. DeKOSKY: While we are on this topic, one of the things that I wanted to clarify was the role of steroid infusion during the course of being on the medication. If I remember correctly, the proposal was that high-dose methylprednisolone in the course of a relapse during therapy would be

allowed, and the question of how to manage that, whether it is considered a second kind of immunotherapy, how many times one might do that through the course of this, and how we would track it is an issue that I think relates to this discussion.

DR. KIEBURTZ: Okay. Dr. Porter.

DR. PORTER: I have been holding back on this question, which I asked yesterday, but I think now that we are talking about treatment, we have to know how they are going to great, and I think that is an integral part of deciding whether or not they will treat in those areas.

What I am referring to actually the last part of the little questionnaire. For example, are you currently experiencing any continuously worsening symptoms that have persisted over several days - eyesight, balance, or strength?

If the patient answers yes, they cannot receive Tysabri. Now, I think we need to walk through this, what this means logically, because this has a huge impact on what kind of therapy the

patient is going to get, because the patient will appear in the doctor's office with an acute exacerbation of MS relatively frequently.

Now, they gave us figures that it won't happen that often, but if you listen to the audience, it happens pretty frequently especially in this population.

Now, the assumption here is that this might not be MS. I mean that is the assumption because we are not going to give Tysabri. The assumption is this has a chance of being PML, which who can say it is not. We discussed this yesterday and there is a huge overlap of symptoms.

So, I think we need clarity on how we are going to treat patients, are we only going to treat patients with Tysabri between exacerbations, and if a patient does have an exacerbation, are we going to treat them as if they might PML, or are we going to watch them to see if PML looks like it develops, or are we going to wait to see if this exacerbation begins to look more like an MS event, and then treat with Tysabri.

I think this issue here is very muddy, and I would like to hear the sponsor address it.

DR. KIEBURTZ: I hear your point. I think part of that discussion needs to happen later, that is, how do we actually--

DR. PORTER: My argument is that if you are making decisions about who is going to be treated, you have to know how the treatment is going to be administered, but then I will yield to the Chair at this point.

DR. KIEBURTZ: I would say the base case of what we should be thinking about, that it is going to be administered monthly, and not in the setting of an acute exacerbation. So, it can't be administered when there is an acute exacerbation.

DR. PORTER: Does that mean that every acute exacerbation will then be looked at as a possible PML event?

DR. KIEBURTZ: That's a separate question. That is what I want to talk about later.

DR. PORTER: Okay.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I would like to condense these questions into my own thoughts especially as somebody who treats many patients with multiple sclerosis, the data that we have suggests that patients with a disability up to an EDSS of 5, we have data on that. We don't have data beyond that, but I think the reality is that there is no trend suggesting there is a safety issue in treating patients who have exacerbating or relapsing disease and higher levels of disability should not receive this agent.

The second point as to who should receive this agent, individuals absolutely, definitely have to have confirmed multiple sclerosis, and I think the only criteria that we have that are objectifiable are MRI criteria.

The third, I would suggest that individuals should try other agents first. There is obviously a decade's worth of experience with other agents. We know the safety profile of those agents well. We don't yet know the safety profile of Tysabri in longer term use.

So, those would be my three caveats - not to restrict to a specific level of disability, not to treat individuals who have unsubstantiated disease, and to require use of an alternative agent first.

DR. KIEBURTZ: Thank you.

Let me go in order. Dr. Jung.

DR. JUNG: I would like to address a couple of comments made by my colleagues, first of all, regarding Dr. Porter's comments. I think that similar to what we see in the use of Novantrone with MS, that you will not see family practitioners or even general neurologists without a large collection of MS patients using Novantrone.

I think that most of the neurologists who currently do use Novantrone are those with a substantial population of MS patients who feel comfortable using that, so I think that the concern that Tysabri would be used relative willy-nilly would be fairly unlikely.

Number two, addressing Dr. McArthur's comments, I respectfully disagree. I think that we

have talked frequently in MS about time is brain, and so you really do need to individualize the treatment of the patients, and if you have someone who is clearly going downhill quickly, that waiting for that person to fail one of the current therapies, given the discrepancy in terms of the efficacy of Tysabri compared to the current therapies on the market would be harmful to the patients.

We have also talked yesterday about the unmet needs of MS patients, and although those of us with large populations of MS patients know that we talk when patients are diagnosed about the four therapies that are on the market, there are substantial numbers of patients--and I don't remember the exact numbers--that we know are not being treated even though there are therapies available, and you have to look at the individual patient in terms of needle phobia. The idea of doing self-injections has really turned a lot of patients away from doing the current disease-modifying therapies.

I know that when I have talked to patients about the idea of getting an I.V. infusion once a month, where they are not the ones who are injecting themselves, that there is that attractiveness to that.

I think obviously, we need to be very careful when we are doing informed consent to talk about the risk of PML as we know in that setting compared to what we know about the relative safety of the current commercially available disease-modifying therapies, but I think that that unmet need needs to be addressed.

We know that there is a substantial number of MS patients out there who are not being treated.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: I think we need to keep in mind that what we are proposing, as Dr. Porter alluded to, is something between a release of a drug and a long-term clinical study, that we are really looking at something that is going to collect data, a mechanism of collecting data over a longer period of time in a situation that we don't

know what is likely to happen in 5 or 10 years.

There are a number of different situations here - has the patient had pretreatment with one of the usual drugs, has the patient had pretreatment with something else, have they had a couple of courses of a blast of prednisone followed by perhaps some other anti-immune drug, et cetera. There are a lot of different situations.

The other point that has come out very strongly recently, and alluded to earlier, of course, is that the earlier you treat, perhaps the better you are able to prevent long-term disability.

I am wonder if we might not have, since the proposal is to be dealing with a limited number of skilled physicians working out of infusion centers that are going to be known to and working with the company, have a series of gradations of patients, groups that are going to agree to take the medication early after a clearly definite diagnosis is made, the people that are going take it later, people that want to try it early, people

that don't want to try it early, but have tried it after many other things.

I think there is a lot of different areas that need to be explored. I don't think we know what the effect on chronic progressive MS is and yet yesterday we heard a number of testimonies saying that this drug worked at least temporarily to chronic progressive MS.

I am not sure how to answer the question.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Actually, I wanted to go back to--I don't know if it was a debate or not--between Drs. McArthur and Jung and see where they disagree.

Dr. McArthur, were you basically saying that nobody without some disability is a candidate? Is that a proper interpretation of what you said?

DR. McARTHUR: That nobody without disability?

DR. TEMPLE: You should at least have some disability before, not just an episode or not just the diagnosis, but some degree of disability, was that your criteria?

DR. MCARTHUR: Let me clarify what I said.

I was actually addressing the other end of the EDSS spectrum, and just to go back to what Dr. Jung was saying, I totally agree with her, and I think the concept of neuroprotection, preventing neural degeneration before it happens, I totally agree with that.

I don't think we have yet any hard evidence as to exactly when that should occur, whether it needs to occur in Year 1 of multiple sclerosis diagnosis, or Year 5, or Year 15, bearing in mind that this is a lifetime process.

DR. TEMPLE: But just to be clear, one could, because of the risk, say fine, we understand getting neuroprotection in early is good, but because of this risk, we don't want anybody who hasn't manifested some degree of impairment, residual impairment treated yet. I am not advocating that. I am just saying one could say that.

One could also say that's part of what a patient and the physician ought to decide together,

how much they want to try to do that. You could also say, well, you should have sure that interferon alone won't do the job.

I mean there is a million different things one could impose, and I guess I should add one could, quote "impose" them with varying degrees of stringency. One could say it is recommended for use in this, one could say it is contraindicated in other people.

These is a wide range of ways to incorporate those views once you decide what the views are. Obviously, this is very important to us.

DR. McARTHUR: Right. So, to answer your question, I don't have any firm ideas of conclusions about at the lower end of the disability scale, because frankly, I think at that end of the scale, the available clinical metrics that we have are pretty imprecise.

I also think it's relatively imprecise to decide whether a patient clinically is having an exacerbation, a new lesion of inflammatory damage

within the central nervous system as opposed to all of the other things that can produce neurological symptoms.

I do think, however, that objectifiable MRI evidence of disease activity, contrast enhancement, there are very few people who would argue with that as being a marker or a metric of ongoing disease activity, and that is why I asked the questions as to whether there was a differential response.

There are only a relatively few number of individuals in the 1801 study who did not have contrast-enhancing lesions. It looked to me, even though the numbers were small, that the treatment effect in that small group was much less favorable for individuals with contrast-enhancing lesions.

DR. TEMPLE: That part seems less controversial. The controversial part is, is there some degree of badness that should be a pre-condition, and if so, do you suggest it, do you require it, do you make someone sign something about it, but we will get to all that.

DR. MCARTHUR: No, I would not set a minimum level of clinical disability for this drug. I think we all see patients who have no disability, but terrible looking scans, and I think those patients should be treated aggressively with whatever one wants to treat them.

DR. KIEBURTZ: I want to move it around, so that we hear from other people.

Dr. Goldstein.

DR. GOLDSTEIN: First, just a point of clarification. We were talking about disability and impairment as if it's the same thing, and there is a difference between impairment and disability.

Impairment is something that I find when I examine a patient. It may be an arm drift, it may be a little problem with coordination, but it doesn't affect activities of daily living or daily life in any way.

Disability is something that impacts on daily life. It is people that can't do their laundry, can't go upstairs, can't take care of their kids, it's that kind of thing. So, when we

are talking about impairment and disability here, we are talking about two different things.

The point that I want to try to make is that, you know, we are going to be talking about a lot of imponderables--well, they are ponderable, but things without answers--because we don't have the data. We can ponder all we want.

I think what we need to try to crystalize is what we really know and what we don't know, and the reason that I think that's so important to do is that if we come down saying that this is something that is worthy of being reintroduced, the people out there need to know, and the physicians need to know, what to have, what the basis is of this risk-benefit discussion.

We don't have good data on people who fail therapy and then switch to a new therapy. That data does not exist as far as I can tell from reading through this.

The data from the 1802 study is not relevant to that because they weren't treated with monotherapy, and we already know from at least the

way the sponsor is proposing this, that monotherapy is not something that they--I mean dual therapy is not something that they are going to proceed, so we don't know that.

We don't have data on people with secondary progressive MS. That data is not here. We don't have data for people with primary progressive MS. Those data are not here. So, as we are talking about, you know, how to frame this and how to frame risk-benefit, I think it needs to be done in a more authoritative way than just having patients and physicians randomly searching the Internet for the next miracle drug and getting misinterpretations of the available data. I think as we frame this, we need to frame it in that setting.

The other point again that I have made several times, I think, is that there are no direct head-to-head comparisons between this drug and the other available immunomodulatory agents, that the data that we are comparing here is data from trials that were done a decade ago to things that were

done relatively more recently, and we are assuming that this difference that we are seeing means that this may somehow be more efficacious than what other drugs are available.

We found time after time after time after time when we try to do that, we are just plain dead wrong, we are just plain dead wrong when we do head-to-head comparisons. So, that needs to also come through that we don't know that that is the case.

I think then people out there and physicians can try to make informed decisions based upon not only what we know, but what we don't know, and as we frame this, who should get what, under what circumstances, I think that needs to really come through very quickly, that we are making guesstimates here.

DR. KIEBURTZ: Let me just take one step back and say that the only reason that we are here, the only reason there is an advisory committee is because there is an absence of data, and I don't think it is going to help us too greatly to

continue to characterize what we don't know.

The reason we are asked to come here is to give our opinion in the absence of data. So, we need to crystalize, each of us in our own minds, what we would suggest, so that these guys can hear it. We are not decisionmakers, we are advisers. They need to hear what we would advise, and if they think we sound like a bunch of loonies, they will ignore us.

If we sound reasonable, they will take our advice, and I am not being critical of you, Dr. Goldstein. I think you are doing a good job of setting up what the issues are, but I also want to drive towards people coming up with their opinion on this, and I think Dr. McArthur has made a good start of that, which is given the risks, we have to be very clear on the diagnosis, we have to be definite on the diagnosis, more than so than we would be with other agents, and we have to be sure that people have definite MS.

He is suggesting that there be MR confirmation of that and that the people have

relapsing as opposed to a progressive MS, so those kind of concrete recommendations, particularly if people disagree with what has been said before, I would like to hear that.

Ms. Sitcov.

MS. SITCOV: Yes, I agree with Dr. McArthur that there must be a concrete diagnosis of MS, but I also just wanted to second something that Dr. Jung said, and that is, I am a Patient Representative and I am here representing patients, and there is a very big needle phobia, and there is a huge unmet need.

I have been injecting intramuscularly for six years, and I close my eyes when I do it, and I get lucky and I hit the right spot, but there is just a very large unmet need, and I have peers who have flat-out said to me--they are not on anything, they have relapsing-remitting, and if this drug becomes available, they will get monthly infusions.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Thank you for letter me speak before I burst. I want to address a couple of

comments. First of all, I think part of what we are struggling with is the heterogeneity of the disease which I think is obvious, but we need to be very careful when we say that you need specific MRI confirmation of MS.

As we know, there is a small percentage of patients with MS who clearly have negative MRs, positive spinal fluid, and so given the conflict that is out there amongst MS neurologists about how to specifically diagnose, we need to be clear about that. Having said that, I understand that we need to be very clear.

The other point I wanted to address was the comment that Dr. McArthur made about requiring MR evidence of active disease. As we know, MR is exquisitely sensitive and one of the things that we need to be careful about is that we don't go over to the other side, which is do we treat the MRI scan and not the patient.

We know that there is frequent changes on MR that are seen when the patient is clinically stable, and so we need to find a comfortable

balance between that in terms of clinical presentation versus MR.

The other point is going back to the comment about failing current disease-modifying therapy. We traditionally tell patients that to see the biologic effects of one of the disease-modifying therapies, that they need to wait six months before we can address whether one of the drugs that they are taking currently is a failure, and again recognizing that time is brain, we need to be clear that we can't use that absolute necessarily on all of the patients.

I think those were my main comments.

DR. KIEBURTZ: Next, is Dr. Sacco, but I am just going to throw in my points since I put myself on the list of things.

I just want to concur with Dr. McArthur that I think being absolutely certain about the diagnosis in an uncertain world is necessary, and although there are possibilities of people having MS with less levels of evidence, just like there are in other illnesses, I think whatever diagnostic

criteria represent the most stringent should be employed here because of the risk of treatment, and the drug as best we know only helps relapsing-remitting multiple sclerosis. That is the only evidence we have. It may help in other things, but we don't have evidence of that, so we have to be very clear that that is who comes in and give practical ways of defining who that is.

I am not expert enough in that to say precisely, but I think that needs to be operationalized in a coherent way.

I think the other thing is based on subgroup analysis it is very hard to predict a clinical subgroup which is going to fare better than others or worse than others aside from the issue of neutralizing antibodies.

That aside, I don't see any demographic clinical or pretreatment characteristics which identify a group of people who are more likely to benefit than others, and we have precious little data above an EDSS of 4, however, a total of somewhere about 120 patients of 4 or higher, so

that starts to define an upper boundary around which we have data, at least the data we are looking at here.

I have to agree with Dr. McArthur, I can't see a lower bound to that. People that are enrolled and eligible all seem to benefit. I have to disagree with him in that I am not certain that there should be a requirement for prior use and failure of other drugs, whether due to lack of efficacy or side effects.

I agree there is a subgroup of people who are non-progressers, who may be exposing themselves to unnecessary risk, but at the point in time that decision has to be made, it is impossible to know who will be these fast and slow progressers as best as I know at this point in time.

As long as those decisions are made with as much information as possible, and that's conducted in a way to minimize risks, I, for one, can't support a criteria of having used and failed other drugs.

Dr. Sacco is next.

DR. SACCO: I also agree with all the comments you made about selecting the right group, and I think Dr. McArthur's points about the MS group is key.

I think the other things we need to be thinking about is when a clinical trial is done, it is set up with inclusion/exclusion criteria, and there are some here that it is worth going back to and reflecting one, because then when a drug gets released, it sometimes gets used beyond that inclusion/exclusion criteria.

One of them was an EDSS has to be less than 5. You couldn't get into this trial if your EDSS was greater than 5. So, I think making sure that we operationalize and make as clear as possible that the inclusion criteria, from the evidence we have in these trials, will be important, and adding to that regarding the diagnosis of MS, because what I am concerned about after hearing yesterday, is that this is perceived as a wonder drug, and it begins to get used in populations that maybe the original trial didn't

include.

That is why I think we are struggling because of the fear of risk from the data we have in the trials that we have in front of us, so making as clear as possible, I think in our inclusion/exclusion criteria, and going back to looking at them I think would be key.

DR. KIEBURTZ: Dr. Koski and then Dr. Temple.

DR. KOSKI: Thank you. You know, one the problems actually is the fact that when a patient is getting towards an EDSS of 4 and 5, very frequently they are beginning to enter into this secondary progressive phase.

So, this has been one of the issues obviously with interferon treatment over the years, because that was also approved primarily for relapsing-remitting, but I will tell you that over time, you know, increasing numbers of patients with the secondary progressive phases actually are on that drug or on those drugs.

So, I think, unfortunately, it's part of

the disease, and I will bet that it will happen, but we can try and limit it by saying that patients under 4 or patients under 5 EDSS, you know, should be the ones that should be considered for the drug.

DR. KIEBURTZ: Dr. Temple and Dr. Katz.

DR. TEMPLE: One encounters this kind of problem all the time. You put people in your trials that you hope you can show improvement in. As they get sicker, you are not sure you can do that.

We don't necessarily always say a drug is only for the people who have been studied. That is a question that arises all the time, and I just want to point out the distinction between telling people who the studies were done in, which is one thing, and literally saying if you are over 4, don't do this.

First of all, I doubt anybody would pay any attention to that, but leaving that aside. Those are two different things. It is a little--I mean I have never treated anybody, but it's a little hard to swallow the idea that as you get

into the places where you are really worried, you stop using the drug that looks like it works rather well. It just seems unlikely to prevail.

On the other hand, telling people where the data came from, even including the patients, to tell them, you know, that is another thing to consider.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I really want to make the same point, but just to emphasize, remember this is presumably, if it is remarketed, it will be done under a very strict registry with forms that the physician will have to sign, which says my patient has disease X.

I mean here, to speak to Dr. Temple's point, we can describe who the studies were done in, but are we really contemplating having the physician sign a form which says my patient has relapsing-remitting MS with an EDSS of 4 or less, is that what we are talking about, because here we are contemplating fairly strict control over who gets it, or at least having people sign forms that

allegedly are truthful.

So, I am wondering are we asking for that sort of documentation in this case, in other words, restricting it specifically to patient who were studied and having the physician affirm on the form that his or her patient meets all of the criteria, the inclusion criteria, is that what we want?

DR. KIEBURTZ: We will see what people say.

Dr. McArthur.

DR. McARTHUR: I already expressed my opinion. I don't think there should be an upper limit restricting the use of this agent for all of the reasons that Dr. Temple just said.

I did want to clarify why I believe that this agent should probably not be used or considered as a first line drug, and just echoing off of some of Dr. Jung's comments, I mean first we have a lot of experience with the available drugs.

We heard eloquently yesterday that many, many patients do not tolerate them well. Many patients have flu-like reactions, et cetera. On

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the flip side, we didn't hear yesterday from the many patients who do tolerate some of these drugs very well for long periods of time.

I think we should not fail to recognize that a monthly infusion of a drug is a complicated process. I am not convinced that the risk management process that is being proposed is going to do anything but make it a nightmare.

For example, I think the last question on the checklist, "Are you current experiencing any continuously worsening symptoms," et cetera, et cetera, I would guarantee that most patients will say yes to that, if they are answering truthfully, and if that's the case, that is going to trigger yet another check with a neurologist or yet another MRI before administration of the drug.

So, this is not going to be an easy process for patients to receive. It is not going to be an easy, one-stop shot monthly infusion, and that is why I believe, in addition to the safety issues, which I do think are tremendously important, the logistics of administering this drug

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should restrict it to, if you will, a second line agent.

DR. KIEBURTZ: Dr. Walton.

DR. WALTON: Yes. Adding on to the aspects that Dr. Katz asked to please ensure to be addressed, another part of what I am hearing, and some differing viewpoints that I would like to encourage the committee to clearly address, is the idea of restricting this to use as a second line drug or not, and that will be an important piece of advice for us to consider.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: I just want to add my comment that I did not believe that the drug should be restricted to people specifically within the lines of the trial, that is, I would not, especially given the fact that it was those with the higher levels of disease activity who appeared to have a better response, at least within the limits of the two-year trial. I don't see a reason to limit it just to people who were in the trial, and would use it for EDSS's who were higher.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: My original comment really had to do with the fact, to just reaffirm, that this really is a spectrum of disease, and one of the problems, of course, is when you really enter into the progressive phase. That is the natural history of what happens with significantly involved MS patients.

I think that then it makes it very difficult to determine on terms of these risk issues, you know, what is going on with the patient, and, indeed, as Justin says, you know, you are going to end up doing probably a larger number of MRIs most likely, and some patients will really object to this more frequent analysis of their spinal fluid.

I think that these things are manageable, you know, particularly in the context of MS centers, but these are all going to be major issues, and I agree to some extent that we may not want to limit the use of the drug to an EDSS of 4 or 5, but I think clearly these patients have to

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have relapses and remissions, so that we have a characterized population, but that might be on the background of progression.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: I guess just to go back, and I guess I would like to concur with Dr. McArthur about the concept of using it as a second line agent simply because, you know, given the fact that people with severe debilitating disease may want to take this risk, I still think that we are very unclear about what exactly the risk is.

Until additional data are available, I think it would be reasonable. We are not limiting the access completely, but we are being a bit more prudent until further data are in.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I agree that I think the diagnosis is most important. I don't agree with the idea of restricting it to second line therapy. In my mind, we will probably get to this later, but the observational study that is being proposed, I am not sure that a huge amount of useful

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information will come from that.

In a sense, I would prefer to see those resources, dedicated controlled studies in some of these populations that we are talking about in concert with a broader RiskMAP program.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Just to follow up on the other comment and agree with, I think the people who are entering into a chronic progressive phase or look like they are beginning to have more frequent relapse are going to be the people that are most likely to be really wanting to have this therapy.

We don't know whether, at that point, you would be able to prevent the development of chronic progressive therapy, so I am just seconding Dr. McArthur's comments that let's don't put an upper limit on it.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Again, just when people comment, it would be useful to know whether or not people think it should--obviously, we are talking about who it should be restricted to or not--but

specific elements of the restriction that people have in mind, it would be very important for us to hear what everybody thinks in terms of must it be limited by severity, must it be limited by as second line, and must it be limited to relapsing-remitting even if it's associated with disability, or does the committee rule out the possibility that it could be used in patients with primary progressive or other forms that weren't studied.

So, relapsing-remitting, disease severity, and second line, it would be useful if people could address those three criteria.

DR. KIEBURTZ: Do you mind--after a little more discussion, I may actually go around on each of those questions?

DR. KATZ: Yes, I think it would be actually useful to go around.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I want to clarify that I am not advocating we treat anyone with an unclear diagnosis of MS, so recognizing that there are

criteria out there that we need to make sure that the patients who qualify for the drug truly do have MS.

I do not agree that this should be used only as a second line therapy for the record.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Two points. One is, or a question actually, can we recommend, getting back to Question 5, can we recommend that a clinical trial be done as part of this approval process that we are at now?

In other words, again, what we don't have to answer, you know, we are battling should it be first line, should it be second line, can we recommend that a prospective randomized trial be done comparing this drug with another established immunomodulatory agent and determine that, get the data for that, at the same time that we recommend restrictions in certain circumstances based upon what we know now? Is that a possible recommendation?

DR. KIEBURTZ: We can make whatever

recommendations we want.

DR. GOLDSTEIN: Is that a reasonable recommendation from a regulatory standpoint?

DR. KIEBURTZ: Let me just point that we already said that we don't recommend anything to make it contingent.

Go ahead.

DR. KATZ: Certainly, there are times when we ask sponsors to do studies after approval, so-called Phase IV commitments, which they agree to, and they are required to complete. So, you can certainly recommend that the sponsor, that we require such a Phase IV study of a particular design, to answer a particular question.

But right, the critical question for us, as Karl said, which is do they need to do that now before we contemplate reintroducing it.

DR. WALTON: Also, a recommendation like that would be useful for us to understand the objective of the study. Much of the deliberation here is related to the uncertainty of the risk of natalizumab, so for any study that you might

recommend, a better understanding of what the primary objective you see from that study and how it might be applied to our oversight over the use of natalizumab would be valuable to us.

DR. GOLDSTEIN: I think I understand. You know, it is getting back to Question 5, was there a study that I thought needed to be done before this was potentially reintroduced in any population, and we answered that question.

Now, what I am saying is that given the things that we don't know, is there a critical question that needs to be answered to try to address these issues that we are debating, that we don't have the data for.

The question I was asking, is that possible from a regulatory standpoint, and the answer was yes.

DR. WALTON: Yes, it is, and you should also understand that we recognize that we only have the data that we have now.

DR. GOLDSTEIN: I understand.

DR. WALTON: That recommendations that we

receive from you at the present time are recommendations for what we should do at the present time, and that as additional data come over the course of the next few years, that changes may well be appropriate one way or another in whatever is recommended or put in place at the present time.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I wanted to go back to the issue--first, I will put on the record that I am not saying this should be second line, because I think it would be available for first line--but I want to go back to this issue of evidence-based recommendations, what is written in your package insert, and what societies will write in their evidence-based guidelines.

I still believe that based on the group in the trial, that is the group that is most likely and should be treated with the drug. So, when Dr. Temple say, you know, well, people may do other things, I agree, but lawyers and other people will read what is written in package inserts, as well as what is written in guidelines.

I think that is where we can at least try to inform both the public, as well as the practitioners, who is the best group to be treated.

The issue is the uncertainty of risk, as well as the uncertainty of benefit, to me, in people with the progressive MS, the group with EDSS above 4 or 5 are progressive. So, I still think that is important, and that needs to be somehow reflected when we think about choosing the MS group for this drug.

DR. KIEBURTZ: I think it should be clear, and you can have relapsing or remitting features with an EDSS of higher than that, you start to get accumulating disability that is progressive underlying it, people still have a relapsing-remitting feature.

I think that gets to your point of if they have that feature, but their EDSS is higher, does that somehow exclude them just because their accumulated disability is higher.

No one has spoken to how they think this should be used in combination with Avonex,

Betaseron, Copaxone, Rebif, and Novantrone. Is that because nobody wants to do that, or is that because you just haven't gotten there yet?

Dr. McArthur.

DR. McARTHUR: We are all terrified. Seriously, i can't believe anybody would recommend that at this point.

DR. KIEBURTZ: I just wanted to get that on the record.

Ms. Sitcov.

MS. SITCOV: I would also be very frightened of using Tysabri with a five-day course of Solu-Medrol.

DR. KIEBURTZ: I think we definitely need to come back to the timing and the co-administration and the management of relapse. We will come back to that. We have to face that at some point. I know Dr. Porter is intimately interested in that.

Do you have something else you want to say, Dr. Porter?

DR. PORTER: Yes, I just wanted to say

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that--and this will surprise you coming from the Industry Representative--that I think that this has to be a second line drug. In the classic administration of medications, we always give drugs first that are safe and effective. This one is less safe at the present time given the data that we have, the limited data.

So, I think we would be, from the standpoint of the point Dr. McArthur made, which is we didn't hear about a lot of people who do well on all these other anti-immunologic drugs, and many of them do, number one, and number two, the medical-legal implications of giving this drug as a first drug before trying something else, I think propels us for sure into saying at the moment, maybe later this won't be true, but at the moment this should not be the first drug that is given to the patient with the disease.

DR. KIEBURTZ: So, can I go through a little exercise here now, which is I am going to ask everybody to answer a Yes or No question, and there is going to be a series of them, and I am

just going to go right around counterclockwise  
starting with Dr. Porter and ending with Dr.  
Hughes.

Bear with me. Just say Yes or No, and  
don't explain yourself.

Would you permit use as a first line  
agent?

DR. PORTER: Non-voting No.

DR. KOSKI: Yes, I would.

DR. GOLDSTEIN: Not now.

DR. DeKOSKY: I would.

DR. KIEBURTZ: I should say your name.

Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Yes.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: Yes.

DR. KIEBURTZ: I vote yes.

So, there you go. No consensus. Sohail will tell us what the numbers were, I presume. I think the point there is you are not going to get a--there is a division of opinion, which I think reflects the reasonableness.

DR. KATZ: Do you actually have a tally somewhere? I realize it's split. I would just like to know what the exact numbers are.

DR. KIEBURTZ: Did you include Roger?

DR. MOSADDEGH: I did, yes.

DR. KIEBURTZ: He's non-voting.

DR. KATZ: Dr. Porter is a non-voting member, but we did ask him, just to get an idea. Give us the tally with and without Dr. Porter. We will figure it out.

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DR. KIEBURTZ: Dr. Porter voted No.

DR. MOSADDEGH: 6-6.

DR. KIEBURTZ: 6-6 excluding Dr. Porter,  
and Dr. Porter voted No.

You missed a vote.

DR. KIEBURTZ: One more time. We missed a  
vote.

Perhaps more slowly. Would you allow  
first line use? Dr. Porter.

DR. PORTER: Non-voting No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: Yes.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Still Yes.

DR. KIEBURTZ: This is a chance to change  
your vote.

Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Yes.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: Yes.

DR. KIEBURTZ: Dr. Kieburtz. Yes.

7 Yes, 5 No. The non-voting is a No.

The second question. Would you impose any limits of functional disability specifically any cutoff scores on the EDSS for eligibility to use the drug?

DR. PORTER: Are you talking the up side or the down side or both?

DR. KIEBURTZ: Either.

Two votes. Would you impose any upper

limit on EDSS severity?

DR. PORTER: Non-voting No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No, but I would want to make  
it very clear that there were relapses and  
remissions. I mean I think that has to be--

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: No.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: No.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: No.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: No.

DR. KIEBURTZ: Dr. Kieburtz. No.

One Yes in the voting group, and the  
non-voting was No.

The same question, different. Would you  
impose any lower--not saying what it is--but would  
you want to impose any lower limit of disability  
scale score on the EDSS?

DR. PORTER: Non-voting Yes.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Abstain.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: No.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: No.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: No.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: No.

DR. KIEBURTZ: I vote No as well.

The tally on that is 10 No, 1 Yes, 1

Abstain, and a Yes from the non-voting member.

One more question. We are making progress.

Do you think MS patients without relapsing-remitting features, that is, with primary progressive MS or solely progressive MS without any more relapsing-remitting features should be allowed to take the intervention at initiation?

DR. PORTER: You mean at this time?

DR. KIEBURTZ: At this time.

DR. PORTER: Non-voting No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: No.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: No.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: No.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: No.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: No.

DR. KIEBURTZ: I vote No, as well.

I think it's unanimous on a No for including individuals who do not have relapsing-remitting features.

Are we getting to things that are helpful for you guys?

DR. McARTHUR: I just think you should clarify that question. It is not so much relapsing-remitting as relapsing, and relapsing progressive, I think would still be encompassed with certainly my recommendations.

DR. KIEBURTZ: Features that include exacerbations.

DR. McARTHUR: Take out the word "remitting."

DR. KIEBURTZ: Would anyone change their vote if we say "relapsing"? I think I am using some different vocabulary, but I don't think anyone changes their vote. I think they can have a

progressive illness, but they still have to have relapsing features.

No one endorses the idea at this point of approval with co-administration of any of the other agents currently approved for the use of MS. The committee was unanimous on that, too.

DR. KATZ: I am sorry. It's unanimous that people believe it should not be co-administered with other?

DR. KIEBURTZ: --approved agents.

DR. KATZ: All other approved agents.

DR. KIEBURTZ: Avonex, Betaseron, Copaxone, Rebif, and Novantrone.

DR. McARTHUR: Chronic administration, because we are still going to have to deal with the issue of methylprednisolone.

DR. KIEBURTZ: Yes. The management of acute exacerbations we have not touched on, but chronic co-administration.

DR. KATZ: And that is because even though we can't say with confidence that the risk is any different with concomitant MS therapy, we are more

nervous that it is, or there is no evidence that those other drugs add anything to the effectiveness of Tysabri? I am just interested in what the rationale is.

DR. KIEBURTZ: I will give you my rationale, and then I will let Dr. McArthur. I think we don't know yet, and it will allow us to get a clear understanding of what the risk is with the agent alone.

There may be circumstances and, in fact, trials where you would allow co-administration, but I would not support marketing, because we don't know yet, and we need a larger sample to get a sense of what the actual risk is.

DR. KATZ: We don't know yet, but we are nervous or you are nervous that the risk is greater?

DR. KIEBURTZ: That is my concern, that there is an enhanced risk with the co-administration of an immune modulator and immunosuppressive agent. Secondly, 1802 suggests that there is--

DR. KATZ: Well, 1802, I think suggest that adding Avonex to Tysabri doesn't really give you very much more.

DR. KIEBURTZ: Adding Tysabri to Avonex, yes.

DR. KATZ: Right, adding Avonex to Tysabri doesn't really give you much more than Tysabri alone. That is a hint, it's not proof, and we don't know anything about what happens when you add any of the other approved MS agents.

DR. KIEBURTZ: Right.

DR. KATZ: I am not advocating a position. I just want to flesh out the committee's thinking.

DR. KIEBURTZ: I understand. So, did that help what I said, and you understand my thinking?

DR. KATZ: Yes.

DR. McARTHUR: My opinion would really just be based on safety issues, but I don't think it is adequate to just list these five agents. I think we need to specify other immunosuppressive agents. They may not be approved for us in multiple sclerosis, but they are being used, and in

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my view, there is the potential for enhanced risk with the co-administration of those agents.

DR. WALTON: We take that point very much. These were listed only because they were the approved agents and might come most prominently to mind.

DR. KIEBURTZ: I think we have had enough discussion on Question No. 6 for the moment.

I think we will take a break for 15 minutes and come back and address Question 7.

[Break.]

DR. KIEBURTZ: Question 7. Considering the currently available data, please discuss whether natalizumab should be returned to the marketplace for at least some patients--and we discussed that without conclusion exactly whom, but with some guidance, I think the Agency can consider--taking into account the preceding discussion of specific populations. After discussion, please vote on this question.

DR. Walton.

DR. WALTON: You may want to decide how

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much discussion you still need, because after all, the previous question had very extensive discussion.

DR. KIEBURTZ: I am not sure we need any discussion, unless I see someone putting their hand up.

So, having done that, and having a full complement, why don't we take a vote on this and we will start with Dr. Porter, who I would like to know even though I know it doesn't count.

So, should we return Tysabri to the marketplace for at least a defined set of patients?

DR. PORTER: Non-voting Yes.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: Yes.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Yes.

DR. KIEBURTZ: Dr Sejvar.

DR. SEJVAR: Yes.

DR. COUCH: Dr. Ricaurte.

DR. RICAURTE: Yes.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Yes.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes.

DR. KIEBURTZ: Dr. McArthur?

DR. McARTHUR: Yes.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Yes.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: Yes.

DR. KIEBURTZ: It's unanimous, 12 to zero,

we vote in favor of returning it to the  
marketplace.

Well, we are halfway there.

So, we have talked about in whom, and I  
think discussion should now continue on a similar  
vein, with not necessarily reaching consensus on  
the how.

Question 8 spans three pages, and it talks

about the essential or nonessential features of an acceptable risk management (minimization) plan. In this discussion, consider the risk management plan proposed by the sponsor and comment on the appropriateness of specific aspects of the proposed plan. Please include in your discussion potential restrictions to patient availability, such as, and then there is Items (a) through (h) with subparts to each of those (a) through (h), somewhere between one and five subparts.

The first question is would we only want patient mandatory registration that is distribution to patients enrolled in the registry. That is what the sponsor proposes, but can we have discussion on that, whether people think that is a good idea or not, or should it be available outside of such a registry.

Dr. Koski.

DR. KOSKI: I would say that it should be absolutely mandatory.

DR. KIEBURTZ: Any disagreement on that?

Dr. Katz.

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DR. KATZ: You could just sort of ask for a consensus. We don't need a lot of discussion I think if everybody agrees.

DR. KIEBURTZ: I think the general feeling is that there should be a mandatory registry in keeping with the sponsor's proposal.

The second part of that is what information should be collected on all patients in the registry, and what you have heard, and I think we heard reiterated this morning, is that the physicians will be contacted by the sponsor every six months for them to relay information about deaths, PML, discontinuations, but then there is other things here - other infections, serious adverse events, concomitant immunomodulator use.

What do you think should be transmitted from the physician to the sponsor at this every six month, what is the minimal essential information?

Dr. Hughes.

DR. M. HUGHES: I guess my feeling here is that mortality, in-depth information about the causes of mortality is probably the most important

information for understanding the risks of this drug in clinical practice.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: I think that if we look at the experience with the NIH stroke scale, which other people at the table can comment about more than myself, it would not be unreasonable to require that the patient have an EDSS recorded on each monthly visit. That would be relatively easy.

Perhaps elements of the multiple sclerosis functional component that they have mentioned, can the patient walk 25 yards, et cetera, et cetera. I think several easy things, these could be done by the staff at the infusion center whether it's a nurse, a physical therapist, a PT aide, whatever, but I think having this kind of information in addition to the mortality, infections, adverse events would be very useful and would provide us with an ongoing database by which you could begin to establish whether this drug is effective over a longer period of time.

DR. KIEBURTZ: Are you referring to the

cohort study or the registry?

DR. COUCH: I am referring to patients who would be in the RiskMAP Registry, every patient.

DR. KIEBURTZ: So, the current notion is that physicians provide information every six months, and you are suggesting every month?

DR. COUCH: I am suggesting that as part of the recordkeeping, when the patient returns, you can do an EDSS very quickly, at least from the impairment/disability standpoint.

You could carry out at least one or two components of the multiple sclerosis functional component, can they walk 25 yards, can they do a few things like that, and then go ahead with the infusion, but this could be done by a trained staff at the infusion center.

This is perhaps not that much different than in the ongoing stroke studies where nurses, technicians, what have you, provide NIH stroke scale data on patients that come in for the JCAHO stroke certification.

DR. KIEBURTZ: Just so I make sure I

understand, so that information would then be held at the site?

DR. COUCH: I believe this information could be recorded and then at the six-month interval transmitted.

DR. KIEBURTZ: Dr. McArthur.

DR. MCARTHUR: I share Dr. Couch's belief that more information is likely to be better, but I am not sure logistically how most infusion centers would be able to do this. I know our own infusion center, I would not feel comfortable that our nursing staff who are very good at what they do, they are not trained to do neurological exams, they are not trained to do EDSS, and I think the variability would really make the data less than useful.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I think the other thing would come up, I mean our own MS center would probably be able to do that. The difference is, however, interpreting that data on a month-to-month basis, because there is variability that occurs, and the

other thing is that, you know, after an exacerbation, you have some persistence of symptoms that, to some extent, resolve.

So, unless you have that all in a linear fashion, I think it would be very difficult to sort of put it together in a cohort type of analysis.

DR. COUCH: I think that would be the advantage of having the linear information to document exacerbations, remissions. I am not suggesting that we are going to look for a linear progression, but we are going to look for what is going on during the time the patients are getting the infusion.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: I guess I would just like to respectfully suggest that the question about efficacy and the question about safety are maybe two slightly different things, and the purpose of the registry, I think should focus on the safety question and kind of focus on that.

DR. KIEBURTZ: Let me just remind people about Slide 94, which is the proposed registry at

least by the sponsor. What the sponsor proposed is any known PML event is reported I think immediately to the sponsor, but then the physicians will be queried every six months for PML, other serious opportunistic infections, death of any cause, and discontinuation.

Those are the only bits of information that would be mandatorily collected on a six-month basis. I believe that is the current suggestion.

What Dr. Couch, if I understand it correctly, is suggesting is that that be augmented by that information being collected monthly along with EDSS and some aspects of the MS functional capacity scale.

Dr. Goldstein.

DR. GOLDSTEIN: I tend to agree that the issue of safety is a slightly different issue than trying to track this information. It may be better to try to track this in the cohort study.

The other point is the list of things to be reported includes concomitant immunomodulators, and it was my understanding from what we discussed

previously, that these folks should not be on concomitant immunomodulators, so I don't know what the purpose is of reporting that. It should be zero.

DR. KIEBURTZ: These questions were written before we voted.

DR. GOLDSTEIN: I understand. So, I think that could come out, but the thing that I would probably put in there is use of I.V. methylprednisolone, because that might be a surrogate indicator for exacerbation, and it is a concomitant medication that may prove important to know about depending upon some of the other risk. So, I would just make that switch.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I think we need to add serious adverse events, because I believe that was not on the RiskMAP.

DR. KIEBURTZ: As currently defined, serious adverse events would not be collected in the context of the registry every six months, but would be in the context of the proposed

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observational cohort, which would be a subset of people.

DR. JUNG: I believe it should be part of the registry, as well.

DR. KIEBURTZ: Other comments?

Dr. Sacco.

DR. SACCO: I think it is important just to clarify the purpose like we have been talking about. We will have the opportunity I think to talk about the cohort where we may be able to get more of the other information that Dr. Couch is mentioning, EDSS score, other risk factors, a larger sample. So, clarifying the purpose, the registry, to me, it sounds like is giving us some safety, but also giving us this connection regarding who the drug should be dispensed to. That is part of the registry, as well.

DR. KIEBURTZ: I think the intent of the registry, as I understand it, is to be able to track this issue almost singularly of PML.

Dr. Temple.

DR. TEMPLE: Just the thought that you may

not want to abandon asking about other immunosuppressives, even though it wouldn't be intended that they be used, because things happen that, you know, you didn't intend. So, someone else, some other neurologist might put them on it and ignore the rules. So, I guess I wouldn't drop that too quickly.

The only other thing I guess I want to say is that hoping that a registry will produce useful effectiveness information is something of a fantasy. They don't really do that.

DR. KIEBURTZ: Dr. Dal Pan.

DR. DAL PAN: Yes. One of the other things we were thinking about with regard to the registry was complete dosing information, so that when we look at whatever adverse events come out, we have some sort of accurate denominator against which to look at the numerator.

DR. KIEBURTZ: And by "complete dosing," you refer not only to doses given in the context of the registry, but any information about prior usage that occurred in trials and in the previous

marketing experience?

DR. DAL PAN: We would be interested in all that, yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Is the intent here that--maybe I am moving ahead to the distribution system--but the registry forms and whatever is decided should be in those forms be received by this central distribution center before drug is dispensed?

DR. KIEBURTZ: I believe the proposed registry, as we saw yesterday, the forms have to be completed before shipment. No?

DR. KATZ: The initial form has to be completed, the acknowledgment form or whatever we are calling it, before the initial shipment of drug, but there is currently in the proposed plan no requirement that there be sort of a real-time--and this is something actually we ask about in one of our questions--there is no requirement that there be some information received back at the distribution center every month before

the next month's shipment is released.

That is a question we had about whether or not that might be more appropriate for various reasons that you can talk about, but that is a question we have. It's not the case in the current proposal.

DR. McARTHUR: So, it seems to me, then, an ongoing cross-check between the receipt of safety information centrally and the dispensing of drugs is critical. No patient is going to enter Tysabri treatment with PML. That is an incredibly unlikely event. It is also pretty unlikely that they will develop PML during the course of Tysabri treatment, but that is the event that we are looking for.

So, in my opinion, we have to link drug dispensing to receipt of patient safety information on a continuing basis not only for as long as the patient is receiving it, but I think for a prolonged period of time after they have received Tysabri.

DR. KATZ: Well, again, that is a critical

element or potential element of the plan that we would very much like to hear what the committee thinks. There are those of us who agree with you and those of us who don't necessarily.

So, we really want to hear a discussion on that specific point, and again I believe it is a specific sub-question a little bit later on, so you can talk about it now or whenever.

DR. KIEBURTZ: We can talk about it now.

Dr. Porter.

DR. PORTER: Good. I think that there is no doubt that you want to have the safety information at hand before you dispense the drug, but I don't think that what you want to do is have an incredibly bureaucratic pass back to the drug company to make sure that they look at the safety data and say, oh, yeah, we agree with, Doc, it's okay to give the drug.

So, I think that it's reasonable to have a safety check, but I think it can be done at the front line with the physician.

DR. KIEBURTZ: Dr. Dal Pan.

DR. DAL PAN: With regard to Dr.

McArthur's point, I just want to mention that Question (c)(4), because it's exactly about Question 8(c)(4), should there be a periodic reauthorization of Tysabri administration, if so, how often? For example, prior to each infusion, every six months, or whatever other recommendation you come up with.

So, that issue is important for us to hear you discuss.

DR. KIEBURTZ: If I understand it correctly, after the initiation procedures, and the registration of the person, depending on how we suggest distribution, it is possible that the person will not be seen by a neurologist for another year, another two years.

There is no mandated reassessment, reevaluation, examination. It is just every six months the physician will be called or contacted by the sponsor and asked do you know anything about PML, other opportunistic infections, deaths, or discontinuations, but that doesn't require that the

physician actually have examined the patient as it stands, as I read it.

Dr. McArthur.

DR. McARTHUR: I think it's an excellent point, and I think it would again, in my opinion, be less than standard of care to prescribe this drug and not follow the patient on a continuing basis or continuing regular basis.

I also, with respect to Dr. Porter, I think placing this just in the hands of busy neurologists, we are notoriously not very good at reporting things on a voluntary basis. I think the FDA can attest to that in terms of their post-marketing experience.

That is why mandating some sort of no form, no drug experience is I guess what I am proposing.

DR. PORTER: Well, I agree with you. In fact, what I was saying is don't make it so tight that every time a dose has to be administered, that there has to be a link back to the drug company, because that will drive everybody crazy. But a

process of reporting the data back to the company,  
I was sort of expecting.

Apparently, that is not part of the plan?  
I thought that was part of the plan, that the data  
that the doctor was going to be collecting on this  
patient would be, as part of the registry, would be  
sent back to the company.

DR. KIEBURTZ: Could you clarify that  
issue for us about the proposal?

DR. BOZIC: We are mandating that the  
doctor provide us with these data every six months  
- the PML, the deaths, the discontinuations, and  
what we have decided is that if we don't get these  
data from the doctor, then, we are going to  
directly contact the patient to obtain the data,  
and if still after that we don't get the data, we  
will de-enroll that patient, and if the doctor  
continuously has a pattern of not giving us the  
data, that doctor will be de-enrolled.

So, we have a mechanism to obtain that  
safety data, and that is our proposal.

DR. McARTHUR: So, how complicated would

it be, Dr. Bozic, how complicated would it be to mandate that, again no form, no drug on a six-monthly basis? You are going to do a lot of detective work. The doctor doesn't send the form back, now you are going to call the patient, the patient is out of town, et cetera.

Why not just make it mandatory every six months if you are on this drug, your doctor needs to provide this form before the drug is released?

DR. BOZIC: I think that what we are proposing is a system that has a great deal of controls in it already. I can walk through all the controls because I think it does bear repeating since I only presented it once yesterday.

So, can I have the slide from my core presentation, please.

[Slide.]

Before the patient and physician start Tysabri, they discuss the risks and benefits. They will read and sign the patient/physician acknowledgment that we circulated today, and then they will send it in to Biogen Idec.

We are going to verify that that document has been signed and that the patient fulfills the criteria, in other words, they have relapsing MS, and then what we are going to do is we are going to sign the patient authorization to that patient, and then we will match them to a registered infusion center.

So, that gives the authorization to that registered infusion center to begin dosing the patient. How does that center become authorized? They have received training by our field personnel on the risks and benefits of Tysabri and the risk management requirements.

The requirements that they have to fulfill are they have to dose only patients in Tysabri Registry, they have to provide a Med Guide to the patient before every dose, they have to complete the checklist before every dose, and they have to document all this in the Tysabri infusion log.

They also receive training on the importance of reporting adverse events to us including PML, and they have to agree to submit to

periodic audits, to verify that they are compliant with this.

So, once an infusion center becomes registered, now they are known to our centralized distribution system, and they can begin receiving Tysabri shipments. So, they can have a small amount of inventory on site, and then once all that happens, the patient can begin receiving Tysabri treatments.

The other mechanisms in the system to facilitate close monitoring of the patient, close clinical monitoring of the patient are, number one, the checklist. The purpose of the checklist is many fold, so one purpose is to make sure that there are no concomitant therapies being used, so we reinforce that.

We reinforce the risk. We make sure the patient has read the Medication Guide, is aware of the contents of the Medication Guide before each dose, and also there is a neurological screening questionnaire to make sure the patient doesn't have any new neurological symptoms that need to be

investigated, and if those are detected, the dose gets suspended and the neurologist gets called in.

So, we have a mechanism to call in the neurologist for cause if there are new neurological symptoms. The other mechanism that we have to facilitate close follow-up with the neurologist is in the Tysabri Registry where we ask for safety information on that patient every six months.

So, that is meant to be a prompt to the physician to, at a minimum, be aware of what the patient's status is. They may choose to have the patient in the office to evaluate that, they may do it by phone. We leave that kind of flexibility in the system there.

So, what I am saying is this is a highly controlled, closed, mandatory system with a lot of regimentation in it already. What you might be proposing, I mean sort of this vial-by-vial sort of distribution model that I believe is coming up in one of the questions, the issue with that is that is very different to how infusion centers operate.

Most infusion centers have a small amount

of inventory on site, and what that allows them to do is to permit scheduling of the patients in some logical fashion. As you saw yesterday, a lot of patients have a lot of difficulty traveling and coming to their visits.

So, you can imagine if a patient shows up for their appointment, for their infusion, and the vial isn't there, that is going to cause a lot of disturbance to that patient, or similarly, if the patient shows up, the vial is there, but the patient hasn't been authorized, these kind of logistical issues are very important in the management and the timing of these infusion centers.

We did a survey also of infusion centers, and we found out that many hospital-based and MS centers, in fact, simply don't want to participate in a model where they would have no inventory on site, because of all these burdensome issues for their patients.

DR. KIEBURTZ: Currently, I just want to reiterate the point you made, that the six-month

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safety evaluation, which is mandatory, and if the physician doesn't do it and the patient doesn't do it, they get disenrolled.

DR. BOZIC: Yes.

DR. KIEBURTZ: The physician can do that in any way he or she feels is appropriate, there is no guidance on that. In fact, they don't even have to contact the patient.

DR. BOZIC: We leave it at the discretion of the physician. I think it would be very hard, as a physician, to give an answer on the status of your patient unless you have actually contacted them.

DR. KIEBURTZ: I think we could make a recommendation to make that clear, that, for example, you can only fill out the six-month evaluation based on an in-person evaluation. I want the committee to know that's the kind of guidance I believe the Agency is looking for.

Dr. Katz.

DR. KATZ: A couple of things. There is at least two issues that are important for us to

hear the committee's views on. One is how often should the patient be seen by the physician. You have just said maybe every six months, and we need to talk about that, whether you want to do that at all. So, that is one thing. That is how often they should be seen by the doctor.

The other is are the elements of the registry, as currently proposed, are they being followed the way they are supposed to be followed. For example, there is supposed to be a checklist administered before each dose.

One question is how do we know that is happening if we think that is an important thing to be done, how do we ensure that in real time that is actually happening. Right now the sponsor is proposing every six months to sort of assess how well the system is working on a number of fronts.

Let me propose a very intensively monitored, restrictive system. It would be useful for us to know whether or not the committee thinks that it is too restrictive or not.

Along the lines of what Dr. McArthur is

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saying and along sort of the clozapine-like, you know, no blood, no drug, no forms sent back to the company or the distribution center, no next vial sent, you just heard why, from a logistical point of view, that might be very difficult to do. You will have to think about whether you agree with that.

But in the most restrictive scenario that I would paint, in order to ensure that the dictates of the registry are being followed, let's say the checklist is being actually administered every month, the company or the distribution center would have to get back a copy of that checklist filled out to ensure that it is being followed appropriately and therefore the drug can be released.

So, that is one sort of scenario, no drug unless you get the forms, as Dr. McArthur put it, on a monthly basis. That would be probably the most restrictive.

One other advantage of at least getting the forms back every month, if not making drug

release contingent on that, but one of the advantages of the distribution center getting the forms back every month is that if a form doesn't come back, the distribution center or the company can call the doctor in real time and say how come no form, how come we didn't get last month's form.

It could be because they forgot to send it in or it could be because the patient discontinued or something happened to the patient. It would be a signal that some follow-up is necessary. So, one scenario would be form sent back or something sent back every month to the distribution center and follow-up to the doctor or the infusion center if a particular month's form isn't returned.

This doesn't require that the drug be released on monthly basis. You could release the drug every six months, let's say, but still require that the form come back every month, and if the form doesn't come back every month, then follow-up, as opposed to waiting for six months, because we want to get this information in real time. If a patient has PML, you don't want to wait six months

to hear about it or something else bad.

So, that's one proposal. It could be electronic, of course, the details to be worked out. So, the question about should a form be sent back every month independent of how often the drug should be sent, it is very useful for us to know what the committee thinks about that kind of system.

DR. KIEBURTZ: Let me make sure I understand. So, imagine a system in which six months' worth of drug is shipped and available at the infusion site, but monthly, in advance of each of those infusions, there needs to be forms.

If those forms are not received electronically, fax, however, by the central distribution center, even though drug is at the infusion center, there would be some feedback to the infusion center you are not supposed to administer to that patient because you haven't given us the information. Is that it?

DR. KATZ: Something like that or just a query why didn't we get the form back, and that

would alert the company in real time with a month's lag that something might have happened to the patient requiring further follow-up. Yes, that's the idea.

DR. KIEBURTZ: Just to expand on that a little and perhaps a conclusion to it, if you then had to have a physician-patient interaction on the six-month basis, the way you get your next six months is that that happened, there is documents that that happened, and the prior six checklist forms also have to be on record, otherwise, you can't get your next six months, so that least you wouldn't have redistribution.

Even if forms aren't coming, it may be hard to stop those infusions, but the maximum you could do is an additional five without forms, because then it would stop based on the next evaluation.

DR. KATZ: Right, and making each monthly dosage, the release of that dose contingent upon getting the forms would be the most restrictive because the physician could not possibly administer

even the next dose because they wouldn't have it.

DR. KIEBURTZ: We have heard some issues about impracticality around that.

Dr. Dal Pan.

DR. DAL PAN: I just wanted to reframe the issue the way Dr. Wysowski framed it yesterday.

So, there is three things that we want to hear about, that are separate but related, and may not be so separate. One is what actually allow the patient to get each dose. Two is should there be periodic reassessments by the physician, and three, periodic reauthorizations, and you can imagine a system where you bundle all that into one or where you separate them. So, that is what we are interested in hearing about.

The second issue is with regard to every six months Biogen Idec contacting the physician about PML and other serious adverse events, opportunistic infections, and our concern was that from the surveillance point of view, that should probably be more frequent. Of course, we would like to hear what the committee has to say about

that, as well.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Just along the same line, I would like to ask Dr. McArthur and Dr. Jung what their feeling is on what the routine follow-up should be for a stable MS patient, how often should that patient be seen in the regular world.

I am assuming that if the patient does have additional symptoms and it looks like they are having a relapse, they are going to come in anyway, but if you have got a stable patient, what would be your recommendation for the length of time between follow-ups?

DR. KIEBURTZ: I am going to let Dr. McArthur speak to that and whatever else he wanted to speak to, and then Dr. Jung.

DR. McARTHUR: I think the issue is not their stability, but we are treating them with an active drug and a drug that potentially has side effects. It looks like the incidence is extremely low fortunately. So, I think initially, in a new entry of this agent into the market, six months

would be a reasonable compromise.

It is not practical for them to see a neurologist every month or two months, and this is probably not necessary, but every six months would seem like a reasonable compromise. If nothing happens in terms of safety issues over the next couple of years, then, we could probably liberalize that.

I would just like to go back to the whole forms issue. You know, this is not rocket science. I mean the forms should be web based. There is no reason to be shuffling paper around the country. The forms should be held centrally in a HIPAA-approved manner.

That means that Biogen Idec and the FDA, and whoever else needs to monitor these things, knows that the forms are being completed relative to the patients who have been registered into the study. I mean to rely on things being faxed around the country is just ludicrous, frankly. It should all be web based.

How you do it in terms of releasing the

drug, whether you have a small inventory for each site with an authorization code, these are all just details that can be worked out, but there needs to be a mandate that that safety information gets back before there is continuing use of the drug.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I believe that given what we have seen with the studies, that with the hypersensitivity reactions and some of the problems that can occur early on in treatment, that probably when you first initiate treatment, seeing the patient within the first three months would probably be appropriate, and then if they are stable, then, going to a six-month period is pretty appropriate.

I am concerned about the idea that from just the logistical standpoint, even for a web-based system, which I think is a great idea, that given the nature of the patients that we are taking care of, to expect them to be able to smoothly receive an infusion once a month based upon feedback from their physician on a monthly

basis is impossible.

You are talking about patients who are traveling in from perhaps rural areas to an MS center for infusion, and the idea that if their doctor happened to not have filled out a particular form within that week, and having the patient turned back is just unacceptable I think.

So, I think monitoring is important, but on a month-to-month basis trying to keep track of that is not manageable.

DR. KIEBURTZ: Let me just clarify. I think what we are talking about on a month-to-month, is that the immunosuppression checklist and the PML checklist is completed prior to infusion, and that is what is sent, so that not a physician assessment, just those checklists although we are going about the content of those, that those are gone through prior to infusion and are recorded.

The physician assessment--and I think you make a reasonable suggestion--it would have to happen before the first dose, at three months, six

months, and every six months thereafter seems like a reasonable schedule, getting back to Dal Pan's question.

But I just wanted to clarify the difference between a physician assessment the pre-infusion checklists, I think we are just talking about receiving the pre-infusion checklists.

MS. SITCOV: Just in terms of the pre-infusion checklist, as a potential consumer in this, I very much care about the safety, but it seems so burdensome to really carry out, because so many of us with MS, in the course of a week can have symptoms that might show up and then remit, and then show up again and then remit, and it doesn't mean that I am having a flare-up, but if I have got to report all of these, and a nurse who is trained at this is perhaps assuming or might be trained to look at any symptom or any change, when am I ever going to get the drug?

I speak of me in the singular. I mean that really generically. It just strikes me as

very burdensome. I wonder if there is just another way.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I would like to actually respond to certain aspects of that question and then one other thing.

First of all, fluctuating symptoms are an aspect of MS, and I think anybody who takes care of MS patients realizes that. The difference is you are trying to look for a progressive type of symptom that has extended over a period of time beyond when the patient has last been seen.

So, I don't think that that type of thing would necessarily, you know, this fluctuating type of symptom would interrupt therapy at that time.

The other thing I wanted to comment on is somebody brought up the issue about a physician, the "neurologist," quote, unquote, that is caring for the patient should perhaps see the patient if there has been an infusion-related reaction.

You know, most of those are going to happen very rapidly, you know, around the time that

you actually get the infusion. Again, I can't speak for all infusion centers. I know with our own infusion center, we actually do have a physician on site. That physician would see that patient for the infusion-related reaction and respond appropriately.

So, it may not be the same person, but usually, that is right at the time the treatment is going forward.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: We are now getting into I think questions of the substance of the questionnaire or the checklist, and we have questions specifically. One of them is up there.

I would just like to know whether or not there is more or less general, before we get to those substantive questions, whether or not there is more or less general consensus that, for example, the requirement that the form be sent back to the sponsor on a monthly basis is something that we should impose.

That is the last suggestion that was on

the table, but I don't know if there is general agreement that that is something that should be part of this.

DR. KIEBURTZ: I agree. Before we get to the substance of the checklist, both about PML risk and immunosuppressant risk, let's talk about the format in which it would be filled out.

Dr. Hughes, Porter, then Temple.

DR. M. HUGHES: My question is on another issue, so I will pass for the moment.

DR. PORTER: My view is very simple, and that is, I have no objection to the concept of having these monthly forms coming back and having it sort of a mandatory process, but I think the forms should be at the infusion center, and if the patient arrives and there is no form filled out, there should be a nurse available to fill out the form, so that they could do it on site, right there on site.

DR. KIEBURTZ: That's the intention.

DR. PORTER: And then the patient isn't penalized for coming 100 miles to get their

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infusion because somebody didn't do it, or didn't do the last one, whatever.

DR. KIEBURTZ: That is where the forms would be. They couldn't be completed in advance or anywhere else but at the time of the infusion.

DR. PORTER: As long as the patient isn't penalized, because the patient is the one that is left holding the bag in these processes, as has been pointed out already.

DR. KIEBURTZ: If it's an authorized infusion center, there should be no difficulty in having the forms and filling them out. That would be who would be an authorized infusion center that they have them and can fill them out.

DR. PORTER: Exactly.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: That is what I was addressing. What I hear people saying about this is that you would learn early whether the forms are not being filled out, but that would not affect the infusion on the day they failed to fill it out. It would remind them that there is something they had

been check, so during the next month, they would call up, ask what is going on, and so on. So, it would really affect that infusion.

DR. KIEBURTZ: No, I mean there is going to be the risk of infusing someone who has symptoms of PML at the time they are infused, because someone may not use the checklist as appropriate.

DR. TEMPLE: But you would know that within a short amount of time.

DR. KIEBURTZ: You would know how many infusions are happening without forms being filled out based on how many don't come back, but it won't prevent that from happening if people flaunt what they are supposed to do.

Dr. Koski.

DR. KOSKI: No, Dr. Temple's comment was mine.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Again, presumably, this would be a web-based system, so that the reporting would be automatic, you fill out the form and the form is reported, so that what you are doing is

looking for a longer term compliance of every six months you review and you say we shipped for this number of patients, and we only have this number of forms, if you are a bad actor and if you don't fix this, we are stopping.

Now, the content, again, that is a different issue, and I think we will get to that later.

DR. KIEBURTZ: I would also just about one of the details here, which I would like to sort of cover (a) through (e) before we go on to (f), (g), and (h), and I think (d) and (e) are mooted actually. I think we are done with (d) and (e). We are only talking about giving this to MS patients who fulfill whatever the restrictions are that you conclude on.

Is that fair? Am I missing some discussion on (d) and (e), which is restriction to only MS patients, restriction to only MS patients deemed appropriate in Question 7? All right.

So, if, in fact, you had a distribution of 6 months' worth of vials, I think it would be

important that those vials be designated specifically for a patient, that the stock you have is not fungible, you can't move it around for a different subject, that it comes, it is for that person, and if they drop out or fail to meet criterion, it would be possible to retrieve those specific vials that were for that specific patient.

What do people think about that?

DR. PORTER: Actually, I think that is a little bit heavy on the bureaucratic side. I think that makes an extra burden on the infusion center and on the sponsor, and I don't think it's necessary.

I think you have got this process. If you have some vials available, it gives the infusion center flexibility, because something is going to happen. Something is going to happen where you need an infusion set for a patient who is right here right now, but you don't happen to have their name on it.

I think that what will happen is that you will end up with people coming to the center, and

they won't have one with their name on it, and this will keep them from getting infused, and it will be unnecessarily bureaucratic.

I don't think there is anything wrong with having, like you have in a pharmacy, a set of infusion packages that don't have people's name on it.

DR. KIEBURTZ: Other comments on that?

Dr. Goldstein.

DR. GOLDSTEIN: A question for the FDA.

You have done similar things. I guess clozapine was one example. How does this work in reality? I mean we are very concerned obviously about putting unnecessary burdens on the patients and on the reporters. At the same time, we want to make sure that the data is being reported and reported accurately.

So, how have you managed these types of things in the past?

DR. KATZ: From the point of view of getting the next week's drug, and again, as Dr. Temple said yesterday, the actual frequency has

changed over time and changes with time, but the patient doesn't get their prescription filled until the pharmacy sees that they have had a blood count taken every week, well, again, every week in the beginning and then it's less frequently over time.

Again, there are provisions that if you meet certain criteria, you have had a case of agran, you are in the registry and you were prevented theoretically from ever getting that drug again, so I think it works pretty well as far as we know.

DR. GOLDSTEIN: And you are capable, and the FDA is capable of monitoring that and you feel that the data that you are getting is reliable and accurate and complete.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Well, just to observe that the burdensome part in some ways, but not an unreasonable one I guess, I would say is the fact that there is a pre-infusion checklist.

Having it be web-based and going to somebody, so they can see if it is being filled out

doesn't really add to the burden all that much.  
That just says you are making sure it happens.  
It's as burdensome as it was before as long as  
people do it.

But we are very mindful of not making it  
impossible to use the drug, so you need to tell us  
whether you think some of these things are  
excessive or not. That is one of the things we are  
interested in.

DR. KIEBURTZ: Go ahead, Dr. Katz.

DR. KATZ: The major purpose of this  
requirement to have the forms be sent back on a  
monthly basis, if that is what you agree to, is not  
to second guess the decision made at the infusion  
center as to whether or not the drug ought to be  
infused at that particular time really.

It is really to see that the process that  
is in place is actually being followed. It is  
really a check on compliance, if you will.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I agree with Dr. Porter. I  
think the practicalities, if you follow the

clozapine model, the pharmacy has a big bottle of clozapine, it is not in an individual patient's name. They just dispense from that bottle.

If we followed that model here, the thing that we want to put in place and make sure that it is happening is the safety reporting on a continuing basis, and if that is left too much to the discretion of the infusion center without any consequences, meaning we have been checking your web-based forms or your paper-based forms, and they haven't been coming back regularly, we are not going to ship your next six months batch of Tysabri.

That is where I would go.

DR. KIEBURTZ: And if you have a pool, the unit of analysis moves from the patient to the center, and there are risks inherent in that, because if a center is not in compliance in general, you amplify the risk, because the noncompliance of a center can be amplified across dozens of patients if they are infusing it improperly by intent or mistake, whereas, if you

restrict the unit of analysis to the patient, the worst you can do is infuse in that person outside.

So, it is a different check and balance. We tend to think of what is the good, but we also have to consider what is the possible in this particular scenario, and there is a risk involved.

Dr. Katz.

DR. KATZ: I have another specific question. Let's say that the forms are required to be filled out monthly and received centrally with that frequency. If a particular form, let's say patients are getting drug for six months, and now on the seventh month, that form doesn't come back, would the committee require the sponsor to call in real time the infusion center and say how come we didn't get the form?

We are talking about going back every six months and sort of seeing how it is going, and maybe won't get the next six, you know, admonishing the infusion center you are not going to get your next six-month supply if you don't fill out the form.

So, I am wondering whether or not, because this is an idea we had floated, that if a particular monthly form on a particular patient doesn't come back, should the sponsor be required to follow up on that, because that could be the first sign that something has happened.

DR. KIEBURTZ: Dr. Porter and then Dr. Koski.

DR. PORTER: I actually think that is probably a compromise that is reasonable as long as it doesn't prohibit the patient who has traveled 150 miles to the infusion center to get their next infusion, but asking the company to follow up every 30 days is not so burdensome, because they should be tracking these anyhow.

I find that an acceptable compromise. What I am really worried about is trying to label the vials with the patient's name, because I think that will fall apart and make life very difficult and a lot of unhappy patients.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: At least it's my

understanding, the way I understood the distribution center, that it wasn't going to go to a pharmacy, that it was going directly to the infusion center.

So, I do think that some type of mandatory monitoring of return of those forms is very important on a regular monthly or bimonthly basis.

DR. KIEBURTZ: We haven't spoken to this, but some level of compliance or rigor in which a center is applying these things might lead to--we talked about deactivating a patient and deactivating a physician, but we didn't talk about deactivating a center.

The amplifying effect of a center problem could go across multiple physicians and hundreds of patients, so I don't believe the sponsor spoke to the criteria for deactivating center, an infusion center.

DR. BOZIC: Our proposal is the infusion centers are attesting that they are going to be doing the checklists, they are documenting that they are doing them, and we are going to be

auditing them.

If a center is noncompliant, they will be deactivated. So, I wanted to make that explicit, as well.

The other thing I wanted to say about this business of vials coming on with a patient's name on it, most hospital pharmacies simply don't purchase drug in that way. They purchase it in small quantities, in this case for natalizumab, but they don't have the patient's name on them, and again it speaks to that notion of having a little bit of scheduling flexibility.

Then, the pharmacy would receive the drug in the hospital, and they would put the patient's name on it and issue it to the infusion center. So again, I just think there is a big burden on shipping on an individual patient basis with the patient's name on it, and I think Dr. McArthur spoke to that, as well.

The last business here is discontinuations due to follow-up, the discontinuations and following up on them. You saw discontinuations in

clinical trials, but those are not reflective of what happens in the real world, and we know from many data that on current ABCR therapy, patients can discontinue at an annual rate of 20 percent, and they most discontinue for all sorts of reasons.

So, we were to follow up, you know, within a month of someone not bringing in a checklist, that could lead to lot of phone calls both to the infusion center and to the physician. Most of those phone calls will end up finding out that the discontinuation was, in fact, not related due to PML, because PML is a very rare event.

So, I guess what I am suggesting is that that is an enormous amount of burden on the infusion center and the physician, when, I think what we are proposing is extremely focused and targeted, and very targeted on the problem at hand.

We have heard from focus groups; from physicians, that if they have a case of PML, they are going to report it to us, and I think that speaks to the nature of the event, the level of concern, the seriousness of the event, and then we

have this additional layer of tracking where we are asking the doctor every six months, on every patient, under penalty of de-enrollment to provide us with those data.

So, you know, we carefully considered all these options, and we believe we found the right balance of, you know, patient protection and also burden and feasibility, and we really tried very hard to find that right balance.

DR. KIEBURTZ: One thing we haven't discussed, but would help address one of your concerns is if when someone discontinues, that that actively be reported rather than retrospectively grabbing that on a six-month look.

That would help issues. It is one of the actually hardest things to know is when someone actually went off treatment, and it would be important for surveillance and understanding the actual cumulative exposure, and that can only be addressed by knowing an end date for treatment.

We are not going to discuss this a whole lot more.

Dr. Goldstein.

DR. GOLDSTEIN: So, what you propose then is to put that as to one of the things that is reported as part of the regularly reported registry information, that if somebody goes off therapy, that that is reported as one of those monthly reports, is that right?

So, it would be information on it, other serious adverse events and/or discontinuing therapy would then be added to those monthly reports, and presumably, there would be some way of saying the reason.

DR. KIEBURTZ: Currently, there is no monthly reports.

DR. GOLDSTEIN: With the infusions.

DR. KIEBURTZ: Checklists.

DR. GOLDSTEIN: Right, with the infusions.

Dr. Jung.

DR. JUNG: We mentioned de-enrollment of centers and of physicians. We haven't really addressed, and I don't think is in the questions, how does one get re-enrolled if one gets

de-enrolled.

We don't want there to be a nominal slap on the wrist if a center is consistently not being compliant, yet, we also need to recognize that we may need to allow some centers to come back and show that they have had improvement.

So, is there a plan that has been thought out about that?

DR. BOZIC: If this becomes the proposal, the accepted proposal, we will work with the FDA on the nature and more details around the plan.

DR. KIEBURTZ: So, let's recap and go back to (a).

So, there is a patient registry, what information would be in that. This is the sponsor contacting the prescribing physician, every six months is the current frequency, to find out about deaths, PML, other serious opportunistic infections, and treatment discontinuations, and we have proposed to add to that other serious adverse events.

There are other things that are in (a)

that we have not talked about including. Use of intravenous steroids is another thing that would be worth tracking on a six-month basis.

Skipping over (b), because we haven't really talked about (b) very much, what the cohort study might be. Regarding restrictions on the distribution system, I don't want to go through each of these things, but have you heard enough discussion about the issues what might be pertinent, or do you want to hear some more specific member-by-member comments on how restrictive this might be?

DR. KATZ: The one thing I think I heard, maybe I wanted to hear it, was that the form should be sent back monthly to the sponsor, and that if, I guess over some period of time, from a given center, the forms are not returned, there is some interaction.

We just heard the sponsor say that following up a particular patient whose last month's form has not been received, following up on a patient-by-patient basis in that way is

potentially problematic. I don't think I know what the committee thinks about whether or not there should be specific follow-up for a specific patient if the previous month's form has not been received back. I don't get a sense of where the committee is on that.

DR. KIEBURTZ: Just to get to that question, for a given patient, should the infusion center and/or the prescribing physician be contacted to be made aware that the required forms that were to be completed prior to infusion were not received on the most recent infusion?

Is that something that should be fed back to the centers and the prescribing physicians?

Dr. Porter.

DR. PORTER: I think what you are saying is reasonable as long as the patient who has arrived on the site isn't penalized.

DR. KIEBURTZ: The infusion is done, they are gone. This is a retrospective. You infused this patient, and we didn't get the forms that you were supposed to fill out beforehand. There is the

implicit threat that if that carries on for long, then, you are going to be deactivated.

The question of how long does that go on for, or how much follow-up, I don't know that we need to get into that.

DR. KATZ: I am actually more interested in not so much the admonition or the threat, but finding out whether or not the patient was lost to follow-up and something bad happened.

DR. TEMPLE: How do they know specifically that an infusion was, in fact, given?

DR. KATZ: How does who know?

DR. TEMPLE: How does the company know?

DR. KATZ: Well, they won't know unless they get the form back.

DR. TEMPLE: No, what I am saying is they don't get a form. How do they know that an infusion was given, but no form came?

DR. KATZ: They don't know what. All they know is that the form didn't come back. The way you follow up, a patient is supposed to get treatment more or less every month. So, if a

patient has been getting it for X number of months, and then the next month's form is not received, there is a number of possibilities.

They decided not to take the drug anymore, that is one possibility. The other possibility is that the patient is lost, didn't come back, you know, is truly lost to follow-up, and you like to find out what happened to that patient.

DR. TEMPLE: So, what they will notice is that somebody who has been getting infusions now is missing a form for a period of time. I guess my gut says sometimes a month might be too short to know. Maybe they were out of the country for a month, and you might have to wait another month.

DR. KATZ: But you could find that out. You would call up the infusion center.

DR. TEMPLE: So, you would have a sort of expected time of arrival.

DR. KIEBURTZ: Once someone has been approved and they are registered, one would anticipate that forms would be coming on a regular basis with some periodicity because either that

should happen, the person has discontinued, died, lost to follow-up, or they forgot to do it.

I think not getting a form should trigger a clarification, what happened here.

DR. TEMPLE: So, as part of the registry, it seems to me they will need to set up some kind of trigger that says if it doesn't show up by blank, I have got a question.

DR. KIEBURTZ: Right.

Dr. McArthur.

DR. McARTHUR: I guess I am missing something here. If my electric company can send me a bill once a month, and if I fail to pay, send me reminder notices, we should be able to have a system that a patient is scheduled for a 10:00 a.m. appointment in the infusion center, they arrive, the pre-infusion checklist is completed.

The patient has the infusion. The presence or absence of infusion reactions are documented, and those data are completed on line during that visit, at the end of that visit, within a 24-hour period into this web-based system.

That gives you, not only the pre-infusion checklist. It tells you that the infusion was done, and it tells you whether there are any reactions to the drug.

What is the problem?

DR. TEMPLE: There is no objection, but you don't know, if you are the company, that the infusion was, in fact, given if they don't report to you. You can only know that you expect an infusion to be given, because one was given two months before.

DR. McARTHUR: Right. So, that would trigger a telephone call to the infusion center to find out if the patient has developed PML.

DR. TEMPLE: I am just saying they are going to have to have an expected date for each patient.

DR. KIEBURTZ: I don't think anyone can disagree with that. I think we did hear some pushback from the sponsor about being concerned about having to initiate the dunning letter to continue the analogy from the electric company.

Dr. Goldstein.

DR. GOLDSTEIN: I was just going to make a similar kind of comment, that this kind of system can largely be automated, and it's an automatic thing. You know, the report goes in, and it's an automatic feedback if the report is missing, and then you get at the end of a certain period of time, a summary report they were missing X number of reports.

Then, you could follow up for the individual patient, but also the surveillance of a center, as well, so it is sort of a double level look of control, but all of this can be completely automated. You know, there is no papers flying around here.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Just the point of practicality. Perhaps as we are designing this form, the ability to mark a couple of things would be helpful and may allow the sponsor not to make a lot of phone calls.

First of all, patients go on vacation, and so if we know that there will be an anticipated

halt to the infusion for a period of time, maybe that can be put in there, so that it doesn't trigger a call.

Number two, the ability to transfer physicians. We know that sometimes patients move from one doctor to the next, so the ability to easily move that patient as opposed to the physician in terms of monitoring might be a reasonable thing to consider.

DR. KIEBURTZ: If you were to follow Dr. McArthur's model, if it's completed at the end of an infusion, if you could indicate the next anticipated infusion date, that would then reset the clock as to when you would next expect a form.

I think we have had enough discussion about those things. We have not discussed two things which I want to do before we break for lunch.

One is there is in addition to the registry, which I remind you is mandatory and for everyone, the proposal to have a more expanded cohort, which would be a subset of people followed

for some period of time with more intensive evaluations in the mandatory registry.

We have already heard from Dr. Hughes some thoughts about that. Maybe you want to reiterate those.

DR. M. HUGHES: I can reiterate some. To me, the registry is really collecting information about exposure and PML, PML mortality, and it would probably provide very useful information on that simply because PML is so rare in untreated patients.

When we go to the cohort study, I am less clear what the real objective is for this study. If it is really to look at SAEs, other infections, and so on, then, I think it is striking to recall that in the two randomized trials that we have looked at so far, the differences in the rates of those events are potentially relatively small, and that's in a controlled setting.

So, it is difficult for me to see that the observational study is going to provide a lot of useful information on those sorts of events in the

absence of having a control group.

I mentioned earlier the idea that maybe instead of the observational study, there should be randomized trials which seek to move into answering some other questions of interest. The alternative is to have a nonrandomized control group in this particular study in which you would collect the same sorts of information about infections, and so forth.

So, I think to me, the observational study as it is currently designed, I don't think it is going to provide particularly useful information in the absence of a control group.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I totally agree with that position. If you design a study, you have to know what question it is you are trying to answer, and I am not entirely clear what question is being answered by this observational study.

On the other hand, as we polled the committee for an earlier question, we were split evenly as to whether the drug should be first line

therapy or not, and there is clearly a major uncertainty about that, and I think that is a major clinical question for physicians caring for patients with this disease, as well as for the patients, as well.

So, rather than investing time and energy for an unclear question, for an unclear reason, I would much rather the effort be put into answering a question that is of direct clinical relevance of importance, which is my view would be that head-to-head comparison as first line therapy.

Then, we will have the data as opposed to debating the data.

DR. KIEBURTZ: Would you like to clarify what the aims of the observational cohort are for us briefly?

DR. BOZIC: Actually, let's just go through my core slide.

[Slide.]

The primary goal of the observational cohort study was to evaluate the safety of Tysabri in the clinical practice setting and over the long

term. We understand the safety of common events, such as all SAEs, I think very well based on the clinical trial data, and we understand those quite well through the end of the two-year period, because that is where most of our data are.

So, what we don't know as well is what will be the safety in the clinical practice setting. So, that is the number one goal of the study.

The other goal of the study is what is the safety overall beyond two years of dosing, and so that is why the study is five years in length.

We can't address the safety in the clinical practice by doing clinical trials, and that is why we are proposing this study. Then, the long-term nature of it, five years again, you only get that in an observational cohort study of this kind.

The second issue that came up was the control group. There are a variety of ways of looking at these data and we are proposing looking at an external control group, a variety of

different ones.

So, for example, we could go back to the clinical trial data and compare back to the clinical trial data, and ask the question, you know, if malignancies are occurring at a certain percentage rate in the clinical trials, now, at what rate are they occurring in the clinical practice setting and over the long term.

So, I think that is one question that we could answer with this study. We could also go back to other databases, like the SEER database, and ask are the rates of events for malignancies over the long term with natalizumab what we would expect based on SEER. So, there are a number of valuable things we could learn from this study.

I think in terms of getting an internal control group, like a disease-based registry, you know, part of the issue with that is, number one, there is a practicality issue that, in general, it can be very difficult to enroll disease registries, because if you think about it, Tysabri-treated patients will be quite motivated to enter in this

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type of study, whereas, patients on other therapies may see less of a reason to participate in this type of study, so there is a practical reason here.

The other reason is that having an internal control group, like in a disease registry, doesn't completely eliminate bias by any means, because the practice patterns for Tysabri may be quite different than they are for the ABCR drugs, and that, in and of itself, may influence the type of safety events that you are observing.

So, an internal control group will simply not eliminate the bias, and that is why we are proposing an open-label design for that.

Finally, let me just go through the next slide, which is the sample size calculation slide, please.

[Slide.]

So, I just wanted to share your thoughts on how we sized this study. We sized this study to look at small increases in rare adverse events, and these could be any types of adverse events, but they are rare events that might not have been

picked up in trials, but which sometimes might be picked up in clinical practice when you treat more patients.

So, what I wanted to show you was that this study is really fully powered to address really very small differences that might occur between the clinical trial setting and in the clinical practice setting.

So, what I have shown you here are the events in clinical trials and the rates of those events as a function of, for example, the serious infections occurred at 1.4 per 100 person years in clinical trials.

This study is fully powered to detect a 1.5 times increase in that rate, which I think is a very conservative viewpoint. Similarly, even for serious opportunistic infections, which I know we are collecting in the overall registry, this study is, in fact, fully powered to look at those.

Those events occurred at 0.07 per 100 person years. I am counting the two PML cases and the Cryptosporidium in the MS placebo-controlled

experience as the rate. That study is fully powered to look at even very small changes in that rate, let alone all serious adverse events, which occurred at an incidence of 7.5 percent annually.

So, what I am saying is this study is very well powered to detect small increases in rare adverse events, and that is why we would advocate for collecting all serious adverse events in this study, but not in the Tysabri Registry, because this study is fully powered to address common serious adverse events.

The last thing I wanted to address was in the Tysabri Registry, I know the committee has made a proposal to collect all serious adverse events on patients. Again, the incidence of serious adverse events in the clinical trial setting is 7.5 percent per year, and what we are talking about collecting are hospitalizations for MS relapses, hospitalization for UTIs, hospitalizations for common bacterial pneumonias.

Our recommendation would be that we can really gain a very good understanding of those

types of events from a 5,000-patient five-year study, and we don't need to do it in the Tysabri Registry.

DR. KIEBURTZ: Thank you.

Dr. McArthur.

DR. McARTHUR: So, you say fully powered.

Do you have actually the power estimates?

DR. BOZIC: What this is, is a probability estimate, because you are comparing between a background rate and looking at your ability to detect a 1.5 times increase in that rate, so it's a 95 percent probability estimate.

DR. KIEBURTZ: I would be interested, I mean I think your inferential abilities regarding what the cause of that increased rate would be rather limited in having an historical group that may have a lot of different characteristics than the treated group, so I am not sure. You could detect a difference, but it would be difficult to know what to ascribe it to.

Dr. Hughes.

DR. M. HUGHES: I guess I would like to

make much the same comment. You are sort of arguing against yourself about using the placebo period of these trials when you think that the rationale for having this study is there may be different rates in clinical practice, there may be different rates over the long term.

DR. BOZIC: But my point is that an internal control group will actually not be that helpful, because you may, in fact, have different patients being treated with Tysabri than patients treated with ABCR.

You know, doctors may choose to use Tysabri in a different way and in different types of patients regardless of the indication statement, and that may influence the safety profile. So, you will still have that difficulty in interpreting the data.

DR. M. HUGHES: I guess at the end of the day, I don't know if this observational study adds a whole lot to the information that is needed to evaluate the drug.

DR. KIEBURTZ: Thank you. I think it

would be a reasonable thing to ask the committee another set of Yes/No questions, or one Yes/No question, which is the following:

Do you think it's crucial for the sponsor to commit to such a cohort study given that we have asked that the serious AEs be incorporated in to the registry?

DR. PORTER: And that you are going to have monthly monitoring.

DR. KIEBURTZ: Go ahead, Dr. Sacco.

DR. SACCO: I think the only thing that is missing in the registry are certain other baseline variables that others have raised before, so when you want to start teasing apart potential factors, risk factors for serious outcomes, the registry may not have the baseline information you need.

So, if we want to have the registry answer that question, then, I think the registry has to be expanded a little bit with certain baseline information to look at either by EDSS, by just other variables that could be predictive of adverse risk.

That is my concern about trying to have the registry do that.

I was going to say for the cohort study, depending on the outcome of interest, I agree for PML, if it's 1 per 1,000 and we have five of them, it is going to be hard to tease out risk factors, but for certain other outcomes, maybe that have a cumulative risk that is a little greater, maybe we will, depending on what baseline characteristics they collect, be able to tease out groups that seem to have a little greater risk depending on the proportionate outcome.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I assume that these baseline factors might be incorporated into that initial enrollment form, and then we would have that data, and you could do those types of analyses.

DR. KIEBURTZ: Remember there is no clinical demographic baseline features. I believe the only thing that is proposed, Dr. Sandroock, the only thing that is currently proposed at entry is

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an MRI, is that correct?

DR. BOZIC: The data collection in the observational cohort study in terms of the demographics of the patient?

DR. KIEBURTZ: No, that is a separate question.

DR. BOZIC: In the registry, it will be just patient name and age and diagnosis.

DR. KIEBURTZ: But wasn't there to be a baseline MRI before initiation of treatment?

DR. BOZIC: Right, we are asking the doctors to give us--well, we are asking that they do the baseline MRI, we are not collecting that information, because that information will be really not very I mean I think relevant to us in terms of just finding the incidence.

DR. KIEBURTZ: You answered my question, thank you.

So, that is the only bit of information unless there is a cohort study, which would gather more information by EDSS and other clinical--whatever else. The registry won't have

that information.

Dr. Koski.

DR. KOSKI: I actually would like to propose that we talk about some evaluations that should be done or what we think ought to be done on patients prior to being placed on Tysabri. I don't think that is discussed in any of the questions. I sort of took a fast look.

In other words, if something in addition to an MRI ought to be done or recommended.

DR. KIEBURTZ: So, (h) is sort of what other potential ongoing monitoring, and I suppose we could add to that baseline monitoring.

DR. KOSKI: Right, I am talking about baseline.

DR. KIEBURTZ: Go ahead.

DR. KOSKI: I mean the thing is that to my way of thinking, I think definitely, you know, an MRI would be absolutely mandatory for a lot of the reasons that we talked about earlier in terms of disease activity.

In addition, I would honestly also feel

that in addition to somebody sort of saying, well, I don't think I am immunosuppressed, I think that things like maybe total lymphocyte counts, perhaps skin testing, as I mentioned earlier, ought to also be considered, and then in addition, and I know that there will be some resistance to this, I think that there ought to be a baseline CSF examination with perhaps some PCR data done.

I know that a lot of that in the beginning, you know, presumably is going to be totally negative, but I think it would be helpful in terms of the subsequent evaluations of patients, those that do have a problem.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: I don't want to interrupt that discussion. I will ask my question later.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: Well, as an old-time neurologist who did a lot of LPs when you had very little else to do, and you didn't have MRI scans. I like LPs, but I actually, in today's world, they are considered an invasive test, and I would have

to know--let me finish--I would have to know for sure that I was really going to get an extremely valuable amount of information that would really direct me toward the process of what is happening with PML before I would be enthusiastic about LPs for patients before they could get what half of you think is a first line drug.

Now, we are doing LPs before the process. I did agree with second line drug. I am against the idea of doing LPs before the drug is given.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I would agree with Dr. Koski that a cerebral spinal fluid analysis prior to initiating Tysabri treatment would be critical. We don't know what we don't know, and we have already heard from the experts that we don't know adequately what occurs in the spinal fluid, and unless we collect that data, we are not going to ever find out.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Using Tysabri is going to be an invasive procedure, and we want to be as sure as

possible, and I think making it as safe as possible, that we have the correct diagnosis is critical. There is a lot of MRI scans that are read as being compatible with multiple sclerosis, that don't turn out to be MS.

So, I would agree that doing the spinal tap with oligoclonal bands or whatever else we could do to try to make certain we have the diagnosis would be advisable.

Secondly, I agree with Dr. Jung that now we have we have another piece of the baseline for later comparison.

DR. JUNG: I didn't mean to say that we should be checking spinal fluid for oligoclonal bands. I meant to say for JC virus.

DR. KIEBURTZ: We previously talked about serum testing for JC virus and learned that it has a poor specificity and in addition to low sensitivity, at least in this situation and in other situations, and I am not sure that CSF improves upon that.

Dr. Clifford, do you want to comment on

that?

DR. CLIFFORD: Yes, I think that it is important for the committee to remember what has been done already.

I, too, love to do LPs, do several a week on a research basis, and I think LPs belong in research settings unless there is a clear indication.

In this case, I would remind you that we had CSF analysis on patients on natalizumab, or actually not on natalizumab, but within three months of the discontinuation of natalizumab, which we know that the biologic effect carries over after the last infusion, so we did a large number, 400 or so LPs on patients in this situation. We found no JC DNA with the most sensitive research assay that we could use.

So, I think that making it a practice to say you must do an LP so that we have this negative substantiated is really an extraordinary idea. I really think it is unrealistic. Further, MS patients, so there was a concern when we started

this business, is there some relation of 1 demyelinating disease with another, of JC with MS, and there was a somewhat confusing paper in the literature that suggested that might be the case.

We contended that wasn't the case, but we are not satisfied with that, and so got these 400 samples from the Karolinska of documented MS patients, looked with the most sensitive assay. These were negative, as well.

I think with 800 samples, carefully looked at including 400 on the drug, that this would be really unreasonable.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I would concur with Dr. Clifford. I think enough is being done with spinal fluid already, not to make this a mandate.

I urged before that there be some attempt to bank serum and although PCR may have limited sensitivity and specificity, we don't know what is going to come down the pipeline in terms of proteomics or other markers. If we don't have the banked specimens, we are never going to be able to

use them, so I would urge that we at least bank serum at baseline.

DR. KIEBURTZ: I think we have heard a couple different proposals regarding what clinical and laboratory assessments might be necessary before prescribing Tysabri, and this particular notion about having to have a JC PCR negative CSF before prescribing it, we have not discussed right now. I have got to say I am a little bit taken aback, I would have to agree with Dr. McArthur and Dr. Clifford that that seems like an excessively high bar to place on access to treatment.

Dr. Rudick.

DR. RUDICK: I just wanted to make a brief comment because it's hard for me to sit without making comments in general, but I have spent much of my career studying CSF in MS for its diagnostic and other value, and I do not agree that you need a CSF to make a diagnosis of multiple sclerosis.

I would recommend that the International Panel, which has worked for several years to establish diagnostic criteria for MS, be the

reference for the diagnosis of MS, and that the neurologists trained in this field be the adjudicators of whether a patient has MS, and I would note that a CSF is not required to diagnose a patient with relapsing-remitting MS by the international criteria.

As a matter of fact, it was required in the prior version for progressive MS, but that was just recently revised and published as no longer required. So, I think that if you required this for diagnosis, I think you would be very arbitrary in that requirement, and it would seem to me to be discriminatory against patients who needed to have Tysabri.

DR. KIEBURTZ: So, to clarify the two uses of CSF, one would be for diagnosis, which I don't think anyone is proposing at this moment, but two would be for some sort of risk reduction, that by establishing that the CSF is negative for JC PCR, that you reduce the risk.

If the best guess of the prevalence of JC PCR positivity in CSF in MS patients is somewhere

around, let's just be generous and say 1 in 1,000, the likelihood of a procedure-related complication, whether hemorrhage, infection, or persistent headache, must be an order of magnitude higher than that. So, I think we need to be careful about a procedure that may carry more risks itself than it would mitigate.

Dr. McArthur.

DR. McARTHUR: We don't have to estimate. We know from Clifford--

DR. KIEBURTZ: Zero out of 800.

DR. McARTHUR: We don't have to estimate. We know what it is, it's zero.

DR. KIEBURTZ: One is within the 95 percent confidence interval of zero, I think, unless we had 20,000.

Dr. Goldstein, Dr. Koski, and Dr. Hughes.

DR. GOLDSTEIN: Again getting back to the point of what is collected at baseline, with all of the caveats that we talked about in terms of the observational study, I don't know that it would necessarily provide an additional major burden to

obtain some baseline data that might help in interpreting these adverse events that we are talking about - age, baseline EDSS score, and whether the patient was on a prior immunosuppressive drug or not.

It is three simple check boxes that we then have the data, and then that again obviates all of the issues we were talking about with the observational study, and then we could again use those resources for other purposes.

DR. KIEBURTZ: Suggesting that as part of a baseline information when you are entering the registry.

DR. McARTHUR: That is exactly right.

Dr. Koski.

DR. KOSKI: Well, I would also just sort of say, I mean isn't it reasonable to have some sort of measures, actually laboratory measures of that, and I knew the CSF was going to be controversial. I just thought it needed to be brought up.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I guess I would make a plea for keeping the registry relatively simple. I think it should be very much focused on the PML question, and if there are particular risk factors at baseline that could be measured easily in that context, I think that is valuable.

Maybe there is a rationale for the cohort study if you are really interested in understanding risk factors amongst treated subjects for rarish serious adverse events that may occur. I still don't believe it is particularly valuable in the comparative setting comparing with historical controls or understanding long-term adverse events in an uncontrolled setting.

DR. KIEBURTZ: I would tend to agree with that and think that although it is an opportunity to gather perhaps some more information about demographic and clinical characteristics of a subset of individuals who are in the treated group, but I continue to think there are going to be difficulties making inferences about changes in adverse event rates that are ascribable to the

intervention because the population will be different than other populations, but it doesn't mean it's not a good idea.

Dr. Sejvar.

DR. SEJVAR: As far as initial baseline work, again, I can think of various immune markers that would be useful to look at, but I would echo Dr. McArthur's suggestion of at least banked serum and blood.

DR. KIEBURTZ: To draw the distinction again, and it's implicit, but maybe it isn't explicit, so I will just say it. The registry is clinical practice. The cohort is clinical research. They are different things. You know, one is going to be what everybody has to do. The second is something that somebody will have to fill out an informed consent and elect to participate in, and questions that are addressable in one are different than the other.

I think Dr. Hughes made a good distinction, which is the registry's intent should not be compromised by additional questions, which

will be less well answered in that setting, and the registry's intent is primarily around this issue of PML and mortality and disability from it.

Dr. Porter.

DR. PORTER: Are we talking about banking samples for the 5,000 patient study, or are we talking about the registry?

DR. KIEBURTZ: Samples would be part of the cohort, not the registry, the research, not the care.

DR. PORTER: Could I ask, you are going to get 5,000 samples then. What are you going to do with them?

DR. KIEBURTZ: I would just say that this committee is not about designing clinical research studies.

DR. PORTER: Well, that is what we are doing, though.

DR. KIEBURTZ: No, we are not.

DR. PORTER: We are drawing blood. We are advocating drawing blood--

DR. KIEBURTZ: We are making advice about

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potential future studies, but we are not designing it, approving it, or anything else like that.

DR. PORTER: My point is that unless we are absolutely certain we know what we are drawing these samples for, that I am not in favor of advocating it.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: I am generally in favor of banking samples because you can't predict the future. I think the last discussion got at what the company was trying to propose, that is, that the treatment part of it, the practice part of it should be kept relatively unencumbered and in order to do more intense looking at something, with all the difficulties that observational studies require, you would identify a group of people and a group of patients who are willing to be more aggressively studied.

So, I hear some tendency to try to include the stuff from the observational study back into the practice part of it, into the registry, and I think the intent was that you should try to keep

them separate, much as Dr. Hughes said, don't make it too complicated to be part of the registry, if you have other questions, study them in the observational study.

Now, the limitations of that study, I think you have all described, how much can you learn from an observational study of that kind, so that is a separate question, though.

DR. KIEBURTZ: You have heard a range of discussion about how much to put into practice including hedging into serious adverse events, which is both a clinical and research thing, and I think that may, based on the discussion, be over-encumbering that registry. It may not, and there may be additional reasons to want to do a cohort that would get at other things that the committee members have expressed interest in.

Ms. Sitcov.

MS. SITCOV: I just wanted to say that I agree with Dr. Hughes. I think that putting in too much is really just an over-encumbrance and a disincentive for the user of Tysabri.

DR. KIEBURTZ: It is 12:25. I am not going to pursue the question about doing a Yes/No vote on that, because I think we have had enough discussion that will be informative to the FDA.

We have not gotten to the checklist. We will not get to the checklist before lunch. I think that is going to be another discussion afterward, but I will consider the discussion on Item 8(a), (b), (c), (d), (e), and that's it, concluded. I don't want to revisit those unless absolutely necessary unless you feel that we have not had sufficient discussion. It sounds like we are doing okay.

I want to come back after lunch and talk about the checklists and then any additional monitoring. Just for the sake of the observers, we voted on Question 7. I don't necessarily anticipate there will be another question that we will vote on.

We may, we may not, but looking at the topics heading forward, there may not be any formal votes. I don't want you to think that I am

precluding them, but just so you can plan your day.

So, with that said, we will adjourn for  
lunch and reconvene at 1:30. Thank you.

[Whereupon, at 12:30 p.m., the proceedings  
were recessed, to be resumed at 1:30 p.m.]

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## A F T E R N O O N P R O C E E D I N G S

[1:30 p.m.]

DR. KIEBURTZ: Just to recap after lunch where we are, we discussed 8(a), (b), (c), (e) and (f), not that there was much discussion on (e) and (f), because that was pre-staged by Question 6, and there was nothing that was voted on, but sort of the overall sensibility was that the proposed information, what the sponsor proposed to be in the registry was necessary.

There was a little bit of debate about whether that was sufficient, whether there should be more materials provided as part of the registry, which would be on a six-monthly basis, but there was no clear consensus on that. I think that is something, the discussion, we will leave up to the Agency and the sponsor to work out the details on that, and similarly, with the observational study, there would be some additional questions that the committee think are worth addressing, that would be appropriate in the context of a research study rather than mandatory as part of clinical care, and

that there should be some restrictions on distribution, but not on a one-to-one basis, and some mandatory monthly reporting back about the use of the checklists and that a feedback mechanism should expected checklists not be received, that that would be evaluated to find out why expected forms were not received, patient finished taking the drug or some other problem.

We also endorsed the idea that there should be some actual in-person evaluation, and in clinical care, that might be something on the basis of baseline three months, six months, and every six months after that, but again, that is not something we voted on. I think there was kind of a discussion around those items. Again, I presume that that is something that will further worked out in details between the sponsor and the Agency.

So, that is where we are. The things that we have not talked about is what those specific checklists would be that have to be completed at the time the patient arrives at the infusion center and is preparing to have the infusion, there should

be some evaluation to check on two things.

One, is there evidence that the individual is or has been immunosuppressed, which would increase the risk, or is there some evidence that the individual may now have signs or symptoms of PML.

I think we are essentially left with the notion that any exacerbation--and I don't mean to paraphrase the sponsor here--but I believe what we heard is that any exacerbation would be treated as if it could be a new case of PML and evaluated as such.

We haven't talked about what that evaluation would entail, but at least we know that that would entail an MRI scan and physical exam.

Let's go back to the checklist, what should be on the checklist, and we have proposals of both, I believe, in front of us about--it's one checklist--about what would be evidence of immunosuppression or risk for immunosuppression and what might be evidence of having signs or symptoms consistent with the development of PML.

So, I would like to entertain some discussion about the proposed checklist.

Dr. Jung.

DR. JUNG: I think as Ms. Sitcov had mentioned earlier, as is common for most MS patients, having waxing and waning of neurological symptoms is a part of the disease, so we need to be able to draw a line between at what point we get concerned.

So, I would propose that we consider changing the language for the last question in the patient checklist to persistent new symptoms or new symptoms that have persisted over perhaps a week or several weeks time as we know that the decline associated with PML is a more subacute, progressive set of symptoms as opposed to symptoms the last several days

DR. KIEBURTZ: There was some discussion or some speculation if there were a subset of symptoms that are characteristic of PML that could be differentiated from the signs or symptoms of an exacerbation of MS.

I think Dr. McArthur, you at least alluded to that that would be a very difficult task because virtually anything could be either.

DR. McARTHUR: I think virtually anything with the exception of optic neuritis could overlap.

DR. KIEBURTZ: Myelopathy perhaps.

DR. McARTHUR: Well, myopathy, but I think from a symptomatic standpoint, it is very difficult for just going on symptoms to distinguish no localization.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: I think maybe temporal profile might be somewhat more helpful, but even that is difficult to separate the overlap, I think.

DR. KIEBURTZ: You mean temporal profile in one sense that it's acuity?

DR. SEJVAR: Right.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Just two points about this. One is I think this needs to go through the usual language correction for people's reading levels as we would normally do for any consent

document. This has a lot of very high level terms here that I think could be confusing or misconstrued or misunderstood, so I assume that is one thing that would happen.

I think the second point that I think comes out here somehow is that this is a surveillance system that has unknown insensitivity and specificity for picking up anything. We are sort of making this up as we go along based upon our best guess.

I think that that needs to come through also, at least in some framework, and that this is something also that is going to be reevaluated as time goes on.

DR. KIEBURTZ: So, just to reiterate that a little. I think that part of the Patient Medication Guide should indicate that by asking these questions, it doesn't reduce the risk of a person getting PML to zero, that somehow by completing this and going through this process, the risk is reduced to nothing.

We would hope that it's reduced, but I

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think it is important to convey the sense that this is an attempt to reduce risk, but we don't know that yet.

Dr. Sacco.

DR. SACCO: I would agree, and I think we could probably sit here for a long time and try to figure out a questionnaire that could perhaps differentiate PML from MS, and it's going to be hard.

I think really from what I understand, if there is any neurological change, whether it's MS or for the PML, that is going to throw up a flag and then they are going to be evaluated further, probably with an MR, so I don't know if we need to really try to tease apart getting this question right for just PML.

DR. KIEBURTZ: And I would propose that. I think the nature of the questions here are is a checklist appropriate. I think everyone feels that we need some document like this. We have already talk about it, that it should be done monthly in advance of each infusion, and that it should be

conveyed to a central area where it would be expected, and its lack of arrival would prompt some action, where is it, what happened, trying to follow up about that.

We have not necessarily talked about who should administer it. I don't think this needs the involvement of a physician or a neurologist. It doesn't need a neurologist, doesn't need a physician.

I think one of the questions would be is it possible to have it be performed by infusion center staff, who are not that necessarily familiar with either MS or PML, and I think that is something that might be useful to talk about.

Dr. Katz.

DR. KATZ: I don't know if you are done with the discussion about how the questionnaire or the checklist should inquire about neurologic symptoms, but recognize that differentiating PML from MS may be very difficult, if not impossible, on a checklist, but it is important for us to know what the committee thinks about that, because if we

say something like any change in neurologic status, we have already heard that that would be extremely burdensome, people would never get their treatments. They would all be shipped off to the neurologist for further evaluation if the question is of that sort.

I know it is hard, but it would be useful for us to know a little bit more about what we think the checklist should say in that specific regard, because we don't want to make it so sensitive that no one ever gets their treatment without first being seen by the doctor.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: One of the other indicators at least of temporary immunosuppression is the appearance of herpes zoster, and would that be something that if the patient shows up with active herpes zoster, which is a pretty common occurrence, should the treatment be withheld at that particular time.

Dr. McArthur.

DR. McARTHUR: I don't think there were

any instances of zoster, or maybe one, in the 1801/1802 studies.

DR. KIEBURTZ: Is it an irrelevant clinical measure of immunosuppression, the occurrence of zoster, I guess, would you want to use it as a sentinel, but to get back to Dr. Katz's question, so we have some discussion about that.

One of the things that I have heard, I believe, is that the persistence of the change would be one thing that would trigger, and perhaps the nature of the change. I think I have heard some discussion about whether it is a change in symptoms or a change in signs, that is, if people have--I guess it is all symptoms until you have an exam.

Dr. Jung.

DR. JUNG: I would like to ask Dr. Clifford, do patients with PML typically respond to I.V. steroids? The reason for bringing this up is I can envision that we would be doing MRI scans on every single one of our patients getting Tysabri on a monthly basis.

Again, given the fact that patients do manifest new symptoms on a regular basis, and given the fact that if you look at the description of the patients that have been described with PML, they had a persistence of their symptoms over a course of time.

DR. CLIFFORD: Right. So, the first question is patients with PML did not normally respond to steroids even transiently. There often are confusions of this sort, and people are given steroids, and PML patients simply don't respond. The one exception to that is something that we are experiencing currently, and that is in the presence of a reconstituting immune system, there are what are called IRIS reactions or immune reconstitution reactions, which are a much more inflammatory form of the disease where part of the symptoms are due to the inflammation.

Those patients may have a partial response to steroids, but PML patients themselves, I think are really quite unresponsive to steroids in my experience.

DR. JUNG: So, would it be reasonable, then, to say that if patients come in with persistent new symptoms, you examine them, you think there may be a possibility that they may be having a clinical relapse of MS, treat them with the standard course of I.V. steroids. If they don't respond, then, move forward to pursuing the possibility of PML?

DR. CLIFFORD: I think that this is something that we have to train and work with clinicians to refine. I think that the company has set up an iterative process where we are going to have to learn how this works in this kind of practice, and I can envision the early part of it having quite a few iterations of people with symptoms coming in.

I think that somebody here was suggesting that some have new symptoms, persistent over at least a few days, and I think what would happen in practice is there to be a signal, and the whole point of this, I suggested this, I wasn't part of the writing or planning for this part of the

process at all, because I was entirely on the Adjudication Committee, but I was asked about what would be helpful, and I said, well, the most sensitive signal in my mind that can be done frequently is to ask for symptoms, because this is not a clinically silent disease for long, and therefore, people do come and tell you there is something different, and families and others, you know, they can't handle their silverware the same way they did, and that is definite, and they can tell you about that before you could possibly do recurrent blood tests, scans, and other things, and I think it is just important to take that seriously even in a patient with MS.

So, the intention here was to bring this to light and to have a clinician then evaluate them, and say, oh, yeah, well, this patient has had this four times in the last five years. Then, you know, they could follow it for another two weeks and see if it went away or give steroids.

If it is the first time they have ever had anything like that, then, I, as a clinician, would

do a scan, and if there were anything strange, I would think about a spinal tap, but I think people will have to learn how to do that.

I think it is important that clinicians, in an interactive process with the sponsor, who is trying to help them to apply this, be allowed to use a degree of clinical judgment, so that it doesn't get out of hand in terms of how sensibly it can be managed.

I think it can be done, but I think that there will be a different learning curve in different places, and folks will be terrified, they will be too casual. You know, I think people will have to work with them.

DR. KIEBURTZ: I will go to you, Dr. McArthur, next, but just to reiterate, the checklist is a screening procedure that would most likely happen at the level of the infusion center, which is going to be hopefully sensitive, but not necessarily terribly specific, but not so horrible that everyone is screening positive, horrible in the sense of its specificity, but that that would

then trigger an evaluation by a clinician who is familiar with the patient, may or may not be in person, probably wouldn't be in person initially, but maybe followed up in person and maybe followed up with more things.

I think we are not necessarily talking about what the post-screening activities are yet. I would like to focus still on what the content of the screen question is, but what happens after that in terms of the interaction between the clinician and the patient over the phone, in person, and what subsequent laboratory testing is decided before that person says no, it's okay, this does not appear to be evidence of PML.

That is another discussion, but right now I want to stay focused on the questionnaire.

Dr. McArthur.

DR. McARTHUR: This is another question for Dave Clifford. My read of these cases, and I did not see any of these cases, is that they presented in a somewhat different way than HIV-associated PML.

I mean typically, HIV-associated PML, we think of clear consciousness, motor deficits, visual deficits, cerebellar deficits, and then only later on is there more of an encephalopathic dementia type syndrome. It is relatively late, but these cases all presented with frontal lesions, panhemispheric lesions where encephalopathy and cognitive dysfunction was an early phenomenon, so could we try and focus the symptoms more on those?

I realize that if PML is associated with Tysabri, it, of course, may not be only associated with frontal lobe lesions, but could we use that somehow?

DR. CLIFFORD: I have counseled against that because I think that it is just not right to try to determine a pattern of disease on three cases, and so I really believe it's safer for us to think about the way white matter, subacute white matter diseases present.

I do think that the cases that have been seen in the setting of natalizumab treatment have been very recognizable as PML cases in the sense of

the tempo in the areas of involvement. I mean they went from a silent lesion to definite clinical symptoms one month late to severe disability by three months, and death by four or five months.

We are not dealing with a form of PML that is very different from what we see in badly immunocompromised patients, and I think it would be a mistake, and the way I led the screening of the entire exposed population was just to assume any definite focal progressive symptom had to be questioned, and I think that is the approach that I would counsel should be engaged by these questions, as well.

DR. KIEBURTZ: I think that characterization of new, focal, and enduring symptoms is a reasonable framework to think about this.

Dr. Sacco.

DR. SACCO: I was just going to emphasize that, as well. I would ask the question, if a patient was coming to an infusion center, and they had this questionnaire, and say it was a relapse,

which is possible, it does occur even though the drug reduces relapses.

I assume then they would not get the infusion, they would have to go to their clinician to decide the next step. So, whether it's a relapse or whether it's PML starting, the clinician gets brought in, and they are not given the infusion.

DR. KIEBURTZ: Correct. I mean the instructions are if it is yes to whatever this question is, the infusion is suspended, and the person is referred to their clinician.

DR. SACCO: So, I go back to saying that whether it's a relapse or it's PML starting, I think that's the appropriate plan for now, that we should be doing, getting clinicians involved in the decision-making process of what the next step is for that patient.

DR. KIEBURTZ: I believe that is what the proposal was.

Ms. Sitcov.

MS. SITCOV: This really illustrates my

lack of medical knowledge, this question, but if someone were to say to me is your immune system suppressed, you know, if they asked me did I have an organ transplant or do I have AIDS or leukemia or lymphoma, I would say no to all of those.

But are there other conditions, and there must be, for example, for about a nine-month period last year, I had C. diff, and does that make my immune system suppressed?

DR. KIEBURTZ: A point well taken. I think it has been alluded to that questions about, that's a qualitative judgment, do you have a suppressed immune system. I think that is what Dr. Goldstein was getting to before. That question is probably not a good one, but asking about specific conditions, HIV infection, AIDS, leukemia, lymphoma, organ transplant, and anything else. I think the Agency can work with the sponsor and what conditions maybe herpes, a recent herpes zoster is one of them, conditions that suggest a compromised immune system. A point well taken.

I think similarly having a sheet of what

would be considered an immunosuppressive or immunomodulating drug, have you taken any of these, do you remember taking any of these in the last month to look at, to say yes or no, and I think similarly recordings, we have already alluded to on the six-month basis, but I think this is not a bad point in time to be asking the subjects have you received intravenous methylprednisolone or other high-dose steroid treatments since your last infusion, yes or no, would be a reasonable thing to be checking here in this context.

Other comments or questions about this?

Dr. Goldstein.

DR. GOLDSTEIN: Just a general question.

Are these forms going to be sent back or will the prescribing physician have access to these forms on each one of their patients? As I understand it, this goes to the central location. The sponsor looks at it, the FDA will look at it, but what about the doc on the ground, does he get these reports on a regular basis?

DR. KIEBURTZ: Currently, the proposal, as

I understand it, is the prescribing physician would be notified about the response to this checklist only if there was Yes to the new, focal, and persistent symptoms.

DR. GOLDSTEIN: Right, and as I read it, it's the patient's responsibility. They don't get the drug. It is the patient's responsibility to contact the physician about it. What I am saying is that maybe this should be another one of these automated things that these forms go to the prescribing physician on some regular basis also, because the patient may or may not decide to call the doctor that day.

DR. KIEBURTZ: I am not sure every prescribing physician would want every form that has No's on it, but some way of notifying the prescribing physician if there is a Yes to the question.

Dr. Katz.

DR. KATZ: Do we think it's the patient's responsibility to contact the physician if the infusion nurse gets a Yes answer? I guess I was

under the impression that the infusion center would take the responsibility to call the physician.

DR. GOLDSTEIN: Yes, and that is why I was raising the question. Around here I think it says the physician should be consulted, but it doesn't say who or under what circumstances.

DR. KIEBURTZ: I would just assume that the infusion center would take that responsibility.

DR. KATZ: The other thing is, just to correct something that you said, Dr. Goldstein, we here don't anticipate receiving these forms. Again, we would have to work out with the sponsor, you know, periodic reports from them to see how this whole system is working, but we don't anticipate getting the forms.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Two things I wanted to bring up for discussion. The first, in general, subjects who have MS come to clinic for treatment by themselves. What about levels of cognition impairment in people who have more severe disease, and whether or not they are able to provide this

sort of information, is that a concern, and how do we deal with it?

The second question, trying to put myself in a--having been a patient relatively recently, so I am having symptoms. I know, I have had the disease for several years, and I know when I am waxing and waning, and I know when I am getting a response, but I am also here to get this drug that is supposed to help keep me better.

Why would I tell you if I want to play the odds against relatively low, hopefully, likelihood of developing a fatal disorder, why would I tell you that I am having these if I know that it means I will not get my medication?

That is the piece I think we haven't discussed. Well, it sort of feeds in, in part, to the cognitive issue although I think it is different from the standpoint of impairment of cognition, but that is one of the things that I couldn't see my way to a clear response of the patient who would say I will pass up getting this medicine especially over the first couple of months

or years while people are so focused on this as a new option, and we probably should discuss that and whether there is a way to have less of a problem with people deciding they won't tell the physician or the nurse, because it means they won't get their drug, and they will figure that out fairly soon. In fact, they ought to be able to read that they won't get their drug, especially for people who know their disease.

DR. KIEBURTZ: So underreporting of these new symptoms or misreporting unintentionally due to some kind of cognitive impairment, we have not talked about and is likely to occur to a certain degree. I think the underreporting is really going to be--I don't know how to address that frankly, other than as long as people are informed of the risk and realize that they are putting themselves at potentially increased risk, but the misreporting due to cognitive impairment, this does presuppose, the checklist presupposes a certain ability to know these things, or come to the infusion with someone who does know them, if you don't come alone.

DR. DeKOSKY: In the perfect world, someone who had enough cognitive impairment, and maybe physical impairment along with it, since they currently bring someone with them who could answer the questions. My question was about the case in which these is someone who, as part of their impairment, doesn't recognize that they have a disability, simply cannot remember, or loses the insight to know that these are important questions to be able to answer.

DR. KIEBURTZ: It is a good concern to which we don't have a concrete solution right now.

Dr. Sacco.

DR. SACCO: Sometime in studies the way you have to approach this is the examiner or interviewer has to make some decision about how cognitively intact the person is to answer the questions, that the person is able to either provide consent or at least answer the questions appropriately, and maybe somehow we have to indicate that. If the infusion nurse, which isn't a physician, isn't doing any mental status, but if

there is some doubt in the ability to answer the questions appropriately, then, the whole system gets defaulted.

DR. KIEBURTZ: That is a possibility. The definitions of that will be tricky.

Dr. Goldstein.

DR. GOLDSTEIN: I think we are getting to the point that we raised earlier, that we don't know what the sensitivity and specificity is of the screening procedure. It is being instituted as the best idea of the best notion that we have right now, but that data, and the sponsor I believe said that, it will be looked at forwardly in an iterative process depending upon outcomes.

The other thing is that there is a check, and that is the physician evaluations at the three- and six-month periods. So, in addition to the subjective data that we are getting, that will be obtained from the questionnaire, there will be objective data from physician assessments also. That will help them also in designing this thing as it goes forward.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes. This is in terms of reporting symptoms at the infusion center where there is the questionnaire administered by a nurse or whomever.

I know from knowing enough people with MS, myself included, that part of the way to successfully cope with the illness at times is the degree of denial, and you can't get away from that. That just has to be added to the equation.

Dr. DeKosky.

DR. DeKOSKY: In a way, I am sorry, I may have confounded the issue of the cognitive status of the person, which I think we just have to deal with, with the issue of what appears to be a relatively strong predilection to not tell you about symptoms if it means you are going to miss your drug.

While we may not be able to solve that, I think the question is whether or not we have way to check on it or some other way to put something else in place that would increase perhaps the

sensitivity to having this.

My specific concern is for people who know their disease.

DR. KIEBURTZ: One thing may be, which was just alluded to, that the exams that follow may pick up things that were not alluded to at the time of the questionnaire completion.

Dr. Couch.

DR. COUCH: One of the problems that MS patients run into may be a slow cognitive decline that continues over a period of time, and perhaps, although the Folstein Mini-Mental Status is not a particularly good instrument--and Dr. DeKosky is shaking his head over there--it has been shown to have a low sensitivity, but good specificity.

If we had that as one of the things that we are evaluating initially, then, perhaps yearly, you might be able to see that there is a cognitive decline, is not a cognitive decline. When the patient reaches a Mini-Mental Status of, pick a number, 25, 27, you then have to have information from other people.

DR. KIEBURTZ: That may be something that the sponsor would want to consider putting into the cohort study, which would help get at it, because people will be completing the checklists. Everyone will be getting the checklists. The cohort gives you the opportunity to look at the veracity of the checklist versus other instruments.

Dr. Koski.

DR. KOSKI: Again, I can only speak to our own infusion clinic, but basically, all of these biologicals, and this includes when Tysabri was being infused, were being administered by an RN.

In addition, we also had the policy that we have a physician on call for the infusion clinic, and the physician saw each patient before they actually received their infusion. It was a brief visit, but you got to know these patients, and I think that reasonable or very good infusion clinics are going to be able to handle this.

Over time, particularly when a patient is coming in on a monthly basis, you know how they are responding, you really do.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: A couple of issues. The cognitive dysfunction associated with MS is not easily picked up even by the most astute clinician, and certainly the Folstein Mini-Mental Status exam is useless when it comes to that.

The idea of trying to do neuropsych testing on every person before they get infused is obviously not possible. I think there are other ways which have nothing to do with the checklist itself, but perhaps going forward to how do we monitor our patients, perhaps with more regularly scheduled MRI scans that will give us some objective evidence of disease would be a better way to sort that out.

That would also deal with the potential for underreporting of symptoms for fear of having the infusion taken away.

DR. KIEBURTZ: So, it sort of edges us into (h) if you guys have heard enough discussion about (f) and (g). Thank you.

So, this regards JC testing in serum or

CSF, MRI, quantitative cognitive testing or some kind of screening instrument and full or brief physical examination or questionnaire. Let me just dissociate two things.

One would be a screen-positive individual would go into clinical assessment, and whatever that might be, we are not talking about that right now, what we are talking about is there some other routine evaluation that would be mandated as part of participation in the registry.

We have said we think it is reasonable to require a physician evaluation before it started, at three months, six months, and six months thereafter. We haven't specified what the contents of that evaluation are aside from what one would imagine is a history and physical exam.

The question is would we propose something more to be required to be part of routine clinical care at any of those time points in everyone receiving the intervention.

Dr. Sejvar.

DR. SEJVAR: I guess even before we start

with that discussion, I mean just a practical question, who pays for all this. Is it the patient's insurance?

DR. KIEBURTZ: That's a question I am not sure we can take up right now, but presumably if it was mandated as part of care, appropriate use of the medication, at least some insurance companies would pay for it, but it would not be considered research optional.

It's the clinical care aspect of administration of the medication. Of course, many patients don't even have insurance, so that means they would be paying for it along with the rest of their care.

Certainly any of these things, MRI, physical exam, possibly cognitive testing, and depending on the outcomes of that, may be part of what happens when someone has new persistent and focal symptoms, which might travel with new, persistent, and focal signs, obviously are going to be evaluated as to whether this is a relapse, potentially treated for that, or possibly PML, and

I think an MRI is going to be part of that, and the question of whether CSF is part of that.

But just moving away from that, to what would necessarily be part of the routine evaluation at zero, three, six, and ongoing six-monthly intervals, is there something besides a neurologist's or a clinician's interview and physical exam that we think would be necessary and mandatory as part of appropriate use of the drug?

Dr. McArthur.

DR. MCARTHUR: This is not in individuals who screen positive on whatever symptoms. This is just routine, everybody is doing fine.

DR. KIEBURTZ: They come back at their three and six months. They have no relapse, no problems, they are doing well. So, it would apply to them equally. This isn't triggered by any event. This is just routine mandatory care.

DR. MCARTHUR: I think the standard of care now for most MS patients on immunomodulatory therapy would be to do regular cranial MRIs, because the question is should they be done more

frequently in individuals on this particular treatment.

DR. KIEBURTZ: Regular means?

DR. McARTHUR: Well, one to two years. I mean there are no hard data at this point as to how frequently or how infrequently one should do them, but I would appreciate input from anybody, including in the audience I guess.

DR. KIEBURTZ: No.

DR. McARTHUR: No? Stay quiet.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I just want to make one point. The way you posed the question was should there be any other routine mandated testing at these time points, and you noted the time points to be three months, six months, and then six months afterwards, which is when I think people thought that the neurologist should see the patient.

The question was meant to be broader than that and whether or not, for example, something instead of the checklist is the only thing that is done every month. The question is should any of

these things be done every month or whatever frequency. I wouldn't limit your thinking about it to the doctor visits.

You may ultimately decide that, if anything, should be done routinely, it should be done at those times, but I wouldn't want to restrict thinking about it at the outset of the discussion to those specific times.

DR. KIEBURTZ: Thanks for that clarification.

DR. MCARTHUR: If I can finish my thought then. So, I mean if I was giving Tysabri, I would want to do a scan every six months.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I was going to speak against any routine monitoring. I mean just as we don't know about the specificity and sensitivity for the questions, I am not sure doing routine MRI scans, say, annually, every six months, or any of these other tests will help us right now, and it will throw a lot more cost into the system.

So, I would prefer, now that we have had

the reauthorization and we have the clinicians being brought into the system every--I think it was at three months, six months, and every six months afterwards, that that alone would hopefully provide a system of detecting either PML or worsening MS.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I believe, first of all, that it is not necessarily accepted as the standard of care that any scan get done every one to two years. There may be regional differences, but I don't believe that that is assumed. We may all have very strong opinions about that.

Number two, I disagree with Dr. Sacco, in that my concern if we are not clear about what the expectations are for monitoring this drug once it is used, is that insurance companies will not readily pay for MRI scans q three months or q six months even if you think it is clinically indicated for a drug like this unless we say that we think this is critical, and I think it is unreasonable to put the clinician or the patient--to give them the burden of trying to prove that they need the study

given the fact that it's readily recognized that there is this risk associated with this drug.

DR. KIEBURTZ: Let me just get back to Dr. Katz's point. I would like to hear from anyone who feels that something aside from the checklist needs to be done on a monthly basis.

Dr. McArthur.

DR. McARTHUR: I don't think anything needs to be done on a monthly basis because frankly, there is no test to identify PML with the exception of MRI and spinal fluid JC virus. We have already discussed that the clinical symptoms and signs are not precise enough to make the differentiation between those from MS, those from PML, those from nerve root disease, those from carpal tunnel, et cetera.

So, if we are not going to do spinal fluid monitoring, which we have already debated and discussed, I would advocate that we need to engineer into the recommendations, regular MRI monitoring. As a clinician, I would not administer Tysabri unless I was allowed to obtain some

objective measure of what was happening in that patient's brain.

I am very concerned about PML and as far as I am concerned, the only way of detecting PML in somebody whom I am administering this drug is by doing serial MRIs. Six months may not be enough, I accept that, but there has to be some practical interval.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I agree with Dr. McArthur, and I would again state that knowing how insurance companies work, because I do reviews of requests for MRs, that unless something is specifically FDA indicated, that there is a very good possibility that that link-up will be disconnected down the road.

So, for the sake of the patient and for the sake of the physicians, who are taking the risk of giving this drug, we need to make sure that there is some mandate associated with that.

DR. KIEBURTZ: So, nothing is being suggested more frequently than every month--that is

the checklist--the only thing we have suggested more frequently than every six months is in the first three months regarding a physician evaluation that you are hearing comments about every six months or some interval of MRI.

Dr. Temple.

DR. TEMPLE: I just want to be clear we know what everybody thinks about, you know, how urgent and how stringent that is.

That is, you got through the every month part, but do you believe, are you advising us that every six months there should be an MRI as a condition of continuing on the drug, or is it a vaguer recommendation than that, that, you know, good practice suggests you might, that is less forceful, what exactly are you recommending?

Then, I have a previous question. Maybe you think you have answered it and maybe you have, and that is, that the physician is going to be seen every six months. Was it your thought that the patient and physician acknowledgment forms would be redone at six months, is that the form, or should

we develop a different form, or what exactly did you have in mind?

DR. KIEBURTZ: We didn't discuss that specific issue.

Dr. DeKosky, then, Goldstein and McArthur.

DR. DeKOSKY: if we can talk about the first one first. I would like to know--this is not my field--I would like to know what it is we are looking for with a scan on people every six months.

Is it that we are looking for nascent PML developing in the brains of those people, and is that the reason we are doing, the recommendation of Justin is that we do scans every six months?

DR. McARTHUR: At least two out of the three cases had lesions which were atypical on their MRI, atypical for multiple sclerosis. So, again, we can't scan patients every month, we probably cannot scan patients every three months. Every six months would be a reasonable compromise.

If a lesion appeared that was atypical for an MS plaque, I think that would be a major trigger.

DR. DeKOSKY: I agree. I may not recall these correctly, but I thought the reasons for the scans were the clinical symptoms that developed, though, rather than a random survey every six months looking for, or that any of them, in fact, were picked up on an incidental scan. It wasn't driven by a behavioral change.

But you are advocating a scan even in the absence of any behavioral change to see if something is rising even with this low incidence. I know it is not easy, I am trying to track your thinking.

DR. McARTHUR: No, it's not easy, and I completely take your point, I mean that the MRIs in the three cases obviously were triggered because it was a neurological syndrome.

I think we are obviously, or I am erring on the side of conservatism and managing patients in what I think is the safest possible way, and the only way I can think of to monitor patients for a nascent or developing brain infection is with cranial MRI that is practical. We can't do spinal

taps, we have discussed that.

I don't know if six months is going to be frequent enough to capture an evolving PML lesion, recognizing the infrequency of that event. That would be my recommendation.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I just wanted to take the same point that was just raised. We have no data at all that a screening MRI scan will, in fact, detect preclinical disease, nor that that detection would change anything.

I take your point, though, that there needs to be some language that doesn't preclude physicians from doing that if they think it is clinically indicated or as part of their own individual care.

So, I think wording to that effect, that MRIs should be obtained for clinically relevant indications, and you may consider surveillance a clinically relevant indication, and that hopefully will take care of the third party carrier issues related to getting it paid for.

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DR. KIEBURTZ: Let me also come back to Dr. Temple's point, which not everyone may see the distinction. Maybe everybody does and it is redundant to say it again. There is a difference between it being recommended, strongly recommended, and required, and I think you are looking for some level of certainty that this must be done on everyone at this minimum frequency.

Dr. Koski.

DR. KOSKI: Like Justin, I basically do think that when you are following an MS patient, just as part of the normal care for them, that I usually get an MRI at least on a yearly basis, and part of it is because sometimes there are silent lesions, you get an idea about the disease burden over time that is going on, and it might indicate a need for a change in therapy.

I think it is very difficult, because I think that the evolution of these lesions probably does occur over one to two months perhaps. Should we mandate each six months, I am just not sure. I certainly think that in patients that do have

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sustained progression during this period of time, we are going to be getting intermittent MRIs, so I guess the issue is the frequency.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: Just getting into the issue of is it a screening MRI, and should we give some thought to linking the MRI with a change in signs and symptoms that are sustained. It gets into the quandary that you are going to end up doing lots of MRIs, but then at least it reduces it to the group of patients that has developed a new persistent sign.

So, just the thought of perhaps--I am not against the idea of doing at least initially for the first few years, making it a requirement to look every six months, but just raising the question of whether perhaps initially, wouldn't it be wise to link the imaging study to the onset or development of a new focal problem.

DR. KIEBURTZ: I think it is highly likely that everyone who has that will get an MRI.

Dr. Sejvar.

DR. SEJVAR: I guess in addition to the level of the individual patient, at which time detection of developing PML may or may not be helpful in the eventual management, but I guess the biggest reason that we are trying to detect this early is sort of to take action on the whole population.

So, I guess that is one of the things that I am struggling with in terms of considering routine MRI, how frequently or whatnot. I mean we are looking for a sentinel event to call the safety of the drug into question.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: To address Dr. Temple's question, I would suggest that the wording be strongly recommend at six-month intervals or as clinically appropriate. I think that gives you enough leeway and doesn't mandate.

DR. TEMPLE: For the MRI.

DR. JUNG: Right.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I was going to emphasize the

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strong recommendation for those that have neurological symptoms, and I guess I would ask is that we are doing the cohort study, I presume, and maybe getting MRIs in those 5,000 patients at six-month intervals for the cohort study under research purposes would be another approach to look at the detection of MRI for detecting PML and other changes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I just wanted to get back to Dr. Goldstein. If we go to our experience with HIV and PML, it is clear that there can be lesions on MR well before there are clinical symptoms. So, in cohort studies that have been done looking at serial MRIs, it is not infrequent to see, if you will, silent PML lesions, and Dr. Clifford might want to address that.

DR. KIEBURTZ: I will take the point. You can get lesions before symptoms.

DR. CLIFFORD: If I could just give a couple of comments on this topic. My assumption is that the MR scan is probably the earliest signal if

you could do them with adequate frequency, that you would see the pathology before you would see the symptoms in a number of people, and that is why we insisted on MR screening of the entire natalizumab exposed population when we were trying to rule out the presence of active PML.

It really bothers me because although I don't know how long before clinical symptoms occur that you can get an MR signal given the pace of development of this disease. My assumption is that it probably is, on average, no more than a few months that you would have an MR signal before you would have clinical disease, which means that at best, you are maybe gaining a month on the screening inventory for how early you might detect a signal if you did this monthly.

Every six months, you are gaining very little from the sensitivity that you have gained by doing the clinical screen, and at a cost of, if there are two scans a year on 2,000 patients to discover one case one month earlier, and what do we have. We don't have a treatment for this

condition. For all we know, it's an all or none, roll the dice, I am sorry you have been the unfortunate 1 in 1,000 that has developed this illness.

Our hope, of course, is that earlier detection, stopping the interference will result in a lesser lesion or perhaps no lesion. That is what we would love to see, but I think we have no assurance of that.

The other thing that I think don't forget. We heard a lot about the troubles access for patients that hate needles, shot, monthly shots are aversive. Well, let me tell you MR scans are not popular among our patients either, and so I think in terms of access and cost for a group of patients, that you are adding a very substantial burden, and I think that given that we have no treatment for the complication we are looking for, and that we would gain on my estimate only a month or maybe a little more of lead time compared to clinical symptom management, I think that is a high cost to pay.

I would be willing to see annual screening for the first two years or something until we have a better feel for this, but I would hate to see legislation of what is not really an evidence-based recommendation on a firm basis.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: My question may not be moot, but what I was going to say is if I were to go on Tysabri, I would want to have MRIs done as frequently as my insurance company would pay for them.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: I think one of the issues with the MRI, just as an additional issue, and that is, there ought to be a protocol specific as much as possible, so that you don't have MRIs that have to have a lot of different protocols, try to get the same protocol for everything, and get it out to all the centers that are handling the patients, so that the data becomes relatively comparable.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Why would we do one

annually? All that does, if it's because they are on the drug, is give us an even lower estimate of the time that we might catch someone in the act of developing a pre-symptomatic lesion.

I think the issue of standard of care for MS patients probably is where we need to leave this with respect to MR. I agree with Dr. Clifford, that is why I was asking Justin for more detail, that this is not a way we are going to catch this disease even if, in fact, we think that there is a chance if we give antiviral agents that we could slow someone down or stop them from developing worse disease.

So, if we say, well, it doesn't make sense to do it every six months because we wouldn't catch people. It makes less sense to do it once a year with the specific intent of trying to catch a lesion. Otherwise, I would say the MRs should be left to the clinicians and their judgment about how frequently to do them to their patients.

DR. KIEBURTZ: I presume, Dr. Katz and Dr. Walton, you have heard enough discussion on this.

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I think there is feelings that range from making strong recommendations to staying with current practice. I am not going to try to strive to derive a consensus from the committee on this. I think you have heard the range of viewpoints. I don't think it would necessarily be productive.

DR. TEMPLE: I agree with that. I still would like to--no, you don't have to answer, you can leave it to us, of whether what you actually had in mind was redoing the enrollment forms or perhaps a modification of them at six months or some period.

DR. KIEBURTZ: So, remember when people enter, there is this process by which--I forget the particular form--

DR. TEMPLE: Well, there is a Physician Acknowledgment and Patient Acknowledgment. That is sort of the vehicle for enrollment.

DR. KIEBURTZ: It would be signed at baseline. Then, of course, there is this screening checklist monthly. The question is at the times that the clinician is actually again seeing the

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patient, should this document be revisited at each of those in-person meetings?

My guess would be that would be a good idea. Does anyone feel strongly to the contrary?

DR. GOLDSTEIN: To be done annually or at every three months, six months?

DR. KIEBURTZ: It should be redone at some time point.

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Okay. That's good.

We are leaving Question 8. There is no vote, there is no consensus. There is a lot of discussion. Just to bear in mind for the committee members and for the public, in this kind of situation, and many times it is not necessary to drive to consensus or vote on something.

These are discussion items and hearing the discussion in a dispassionate forum is useful to the Agency, and the fact that there is disagreement and lack of consensus doesn't mean people haven't thought about it. It means that is where we are, and I think that the Agency and the sponsor, having

heard that, can negotiate in good faith on what makes sense.

Question 9. For subjects who have received natalizumab in clinical trials, and who have not received for at least a year or longer, do you recommend any further monitoring? That is, people who were in trials, who have now been out for at least a year or longer, should they be monitored in any further way, and if so, how and for how long?

This kind of ties in with the next question. What happens to people who now that it is going to be, presuming our advice is--well, let's just say in the world in which it returns to marketing, what happens when someone discontinues, how long do you monitor them after that?

So, for example, the registry kind of evaluations, which are to be done on a six-month basis, would you continue to do the registry kind of evaluations on a six-month basis or some less frequent basis getting those kind of endpoints, and if so how long would you continue to do that for?

Again, I think the notion behind this, I presume is that the risk of PML does not cease with the ceasing of the intervention, and you would need to continue to follow people who are at risk for some period of time to see if the event occurs. Do I have the reasoning right?

Dr. Sejvar, did you have any thoughts on that?

DR. SEJVAR: I guess I would just like to offer that the answer to both of those would be yes. I mean again, I think that the National Death Index provides one avenue for that, but again there is going to be a significant time delay associated with that.

So, I think that some sort of real-time follow up of patients who have come off the drug is necessary, and then I guess the question is how frequently, and I would think maybe once, you know, a yearly follow-up is reasonable.

DR. KIEBURTZ: I would tend to argue the annual follow-up. Again, the reason for more frequent evaluation and follow-up is to try to "nip

in the bud" or identify incipient or early cases with the idea that discontinuation of the drug might have some favorable impact, none of that being known, but a reasonable hypothesis.

Here, the intervention has been terminated, there is no point in trying to intervene earlier or stop it, but following the group on an annual basis, I think less an annually, you have a higher risk of not getting the information again, but the question is if you did it annually, how long do you do it annually for, two years, three years, five years. I mean you have to do it for some period of time.

I don't know if anyone has any thoughts on that.

Ms. Sitcov.

MS. SITCOV: My feeling is--did I read in the FDA response, your recommendation was five years?

DR. WALTON: No, we did not make any recommendations on that length of follow-up.

DR. KATZ: In the observational study, I

think the sponsors are going to follow patients for five years.

DR. WALTON: But that was for patients who were getting--

DR. KATZ: Continuing on the drug.

DR. WALTON: Continuing natalizumab, yes, or within that study, those who had discontinued it.

DR. KIEBURTZ: Do you want to comment, Dr. Dal Pan?

DR. DAL PAN: I believe in the observational study, it was following people for five years after they had discontinued natalizumab.

DR. WYSOWSKI: After starting Tysabri.

DR. KIEBURTZ: After starting. Okay.

Just for the record, we are trying to sort out what--

DR. McARTHUR: Three years sounds like a good number.

DR. BOZIC: May I just clarify?

DR. KIEBURTZ: Clarify about what?

DR. BOZIC: The length of follow-up in the

observational study.

DR. KIEBURTZ: I don't think that is the question. Thank you, though.

Does anyone feel that evaluation less frequently than annually is appropriate? Does anyone feel that no follow-up after discontinuation is appropriate?

[No response.]

DR. KIEBURTZ: Do you need further discussion on that?

DR. WALTON: I think some sense of how long you feel that that annual evaluation should continue would be useful to us.

DR. KIEBURTZ: Beyond the discussion of two, three, to maybe five years?

DR. WALTON: I wasn't sure if that was the general consensus.

DR. KIEBURTZ: Okay. People's thoughts on how long that might--I mean at some point, the risk of PML from the intervention must dissipate.

DR. McARTHUR: It is quite likely if somebody discontinues this agent, that they will go

on to another agent, which might be even more of a potent immunomodulatory drug. Again, I think we have to be practical. Five years would seem like a good time period to me, but I think we have to compromise a little bit, so three.

What can we say? There is no data to say how long.

DR. KATZ: I think we understand the conversation.

DR. KIEBURTZ: Back to 10(a). Do people feel any differently about discontinuing in the setting of marketed use versus previous clinical trials, or should it apply the same way? It's the same, okay.

So 10(b). If a patient discontinues and plans to initiate treatment with another immunomodulatory agent, should they have a pause before initiating that treatment? If so, for how long should that pause be?

Dr. Jung.

DR. JUNG: I guess it depends upon the reason for discontinuing the drug. If

discontinuation is due to adverse events, then, can you afford to wait a prolonged period of time before starting another agent if the patient is relapsing. So, I think there needs to be more clarification.

DR. KIEBURTZ: Other comments?

So, following up, more clarification in what way, Dr. Jung?

DR. JUNG: I am sorry?

DR. KIEBURTZ: You said there needs to be more clarification of the question?

DR. JUNG: Is the reason for discontinuation because the patient is failing versus is the reason for discontinuing the drug because the patient has adverse events to the drug itself. That would push you towards two separate paths in terms of where the patient is going.

DR. KIEBURTZ: Bear with me. So, say it is because they are failing, would you want to impose a waiting period?

DR. JUNG: I don't know the answer to that. I think it is something we need to discuss.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Are we also talking about steroids here, or is it just other approved drugs for MS? In the example I would raise, if somebody is failing and having a relapse and they are going to come in--

DR. KIEBURTZ: Let's take relapse aside. I mean I think you have to treat a relapse as you treat it, but I think failing in terms of having a number, not the acute treatment of a relapse, but that they are having progressive disability or having a high relapse rate, and you think that you want to shift to a different drug.

DR. KATZ: Just for clarification, I think this is sort of the reverse question that we talked about before, which is if you want to start Tysabri, how long do you have to be off some other immunosuppressant. I think this is just the reverse side of that coin because of the risk of--how long do you have to wait before starting another drug after coming off Tysabri because of the potential risk for PML, to be seen in the

context, you know, the potential increased risk to be seen in the context of essentially concomitance.

I don't think we were looking for the various different reasons, the different waiting periods depending upon the reason the drug was discontinued. It was this question of when do you think the risk of PML dissipates, and I quite frankly don't know how you would answer that question, but that is what we were trying to get at.

DR. KIEBURTZ: Thanks for that.

DR. McARTHUR: You have asked an unanswerable question.

DR. KIEBURTZ: It's a very steep path. I think, though, that the context is if somebody is doing badly on the treatment and you are stopping it in anticipation of shifting to another treatment, there is a little bit more pressure to be able to start the other treatment in the setting of clinical failure of clinical poor progression as opposed to if someone has been very stable and say they develop neutralizing antibodies and you decide

they need to come off, but they have been quite stable and they come off, you might be able to pause more leisurely before you start another treatment.

So, I think there is some point in making that difference. It is going to be very hard to have someone who is doing badly, who you say, okay, we have got to get off of this, and then say, well now we are going to wait a year before we initiate treatment, or two years, or three years. I don't think that is plausible or necessarily defensible because then the accumulating disability sits in contrast to the increased risk of PML that might happen, theoretical increased risk of PML that might happen with the co-administration of another immunomodulatory drug shortly afterwards.

So, I think we do have to think about that. I think if the person is stable and doing fairly well and has to stop, or just decides they don't want to take it anymore, you have a longer period of time where you might wait.

But is there some minimum period of time

you should be forced to wait in the setting of clinical deterioration causing switching off the drug?

Dr. McArthur.

DR. McARTHUR: I think what you have just described is really an argument for making it just clinical judgment, and there is so many scenarios, there are so many reasons why one might wait or one might accelerate a switch, it just has to be part of clinical judgment.

I don't think any of us have any data whatsoever to say three months is safe, but two and a half months is unsafe.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I think what I would fall back on is what we have data for, and that's the way the 1801 trial was done. About 30 percent of them were on prior immunomodulatory drugs, and there was a washout period, I think--is that right, that was required--before they could start on this drug.

That is the only data we have, and we

think that that is relatively safe doing it in that setting, so I would extrapolate and say, well, if you had to pick a number, that's the number I would pick.

In terms of the urgency, I agree you don't want to wait. On the other hand, we also have no data that acute administration of this drug alters the acute exacerbation, so I think balancing those two together, I would just use the same protocol that was used in the trial. That is what we have some data for at any rate.

DR. KIEBURTZ: Two weeks?

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Part (c) is going to be the question which will probably be the most pressing immediately after this goes on the market is anyone who is on ABCR is going to want to know how long do they have to wait before they can take Tysabri, and is there some minimum period of time. Two weeks, is that long enough?

DR. GOLDSTEIN: Again, that is the only thing that we have data for.

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DR. KIEBURTZ: I understand. I am just seeing if there is any difference of opinion. I don't know enough to have a difference of opinion, but I would tend to think that a little bit longer may be a little bit better, but not a lot longer.

Dr. Sejvar.

DR. SEJVAR: I guess maybe at the bare minimum, understanding that there is an effect that sort of outlasts the pharmacokinetics and pharmacodynamics, but couldn't we use those parameters as a bare minimum, or is that where that two weeks came from?

DR. KIEBURTZ: I think we heard that, you know, as Dr. Sandrock alluded to, you can actually do some in vitro analysis of how long the pharmacodynamic effects are, but are there more sort of elusive measures of immune function that might be suppressed for longer periods of time, that when you start to co-administer Tysabri, those increase the risk.

I think this is very hypothetical, and just sort of a clinician sensibility that maybe a

little bit longer to let things wash out before you start something else, but that may be overly cautious.

Ms. Sitcov.

MS. SITCOV: I think it was I who asked the question yesterday about how long one needs to wait, and you mentioned two weeks, but I don't understand why two weeks versus three weeks or five weeks.

DR. KIEBURTZ: Are you addressing that to Dr. Sandrock?

MS. SITCOV: Yes.

DR. SANDROCK: So, if the question relates to how long after stopping Tysabri, when we could restart--we said two weeks based on the PK and the pharmacodynamic effects of interferon, which you can measure for at least a week after an injection based on interferon-inducible genes, we felt that two weeks was reasonable.

If you would like me to address the other, I will.

DR. KIEBURTZ: Do you think there is any

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reason to think based on any information you have that the immunomodulatory effects of interferons last longer than two weeks?

DR. SANDROCK: Well, there is not a lot of data on that. Everything that I just based the two weeks on is based on pharmacodynamic measures.

DR. KIEBURTZ: Actually, since you offered, I will take you up on it. The other way around?

DR. SANDROCK: In the case of washing off of Tysabri, the drug is given every four weeks, because we maintain saturation of alpha-4 integrin receptors for the dosing interval, and we see saturation levels falling at about eight weeks. So, eight to 12 weeks would be our recommendation after the last dose of Tysabri.

Again, that is based on pharmacodynamic measures that we can look at.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Also, we have been talking about the washout after one comes off an interferon, and two weeks was the number that the

sponsors proposed based on dynamic considerations, but there are other immunomodulating drugs that patients may be on. They may not be approved for MS, but they may be on for MS. How long one should wait to wash those drugs out presumably varies with the drug, I would assume.

So, you could suggest that it is drug dependent, you know, you would have to know something about the pharmacodynamics of each of the potential drugs the patients might be on, and say for azathioprine, it is this long, for CellCept it is that long. That is one approach.

DR. KIEBURTZ: I am not sure exactly what Dr. McArthur meant by clinical judgment, but it may be in part that there is not going to be one answer for any drug, it is going to have to be in the context of what is known about the drug, but on the other hand, that will leave the door open for just about any interval.

DR. TEMPLE: It also seems worth noting that in the cases that did occur, it took something close to two years of both of them being given

continuously for anything to emerge. It is hard to think that a week or two of common exposure would do the same thing, but we, of course, don't actually know that.

DR. KIEBURTZ: Sufficient discussion on 10? Oh, Dr. Koski, I am sorry.

DR. KOSKI: That's okay. I really don't agree with--excuse me--I do agree with the two to three months, but I think the other thing is presumably, if you are removing the patient because they are not doing well, or not performing adequately, you are going to have MRI data that will help to confirm at least that none of the lesions at least are similar to PML.

So, I think that will also help to make that decision as part of your clinical decision.

DR. KIEBURTZ: I think that is a good point. So, those are patients who are going to have more extensive evaluation, and that may shape your risk about or your thinking about risk about initiating other treatment.

We will move on to Question 11. I think

the nub of it is if in the previous discussion, you have advised reintroducing the marketing and have suggested only monotherapy, which is what we suggested, please discuss if and when exploration of the safety and efficacy of concurrent use with beta-interferons should be evaluated - never risk it, evaluate it in concurrent clinical trials, only after the risk of PML or other infections is better quantified, evaluated in a concurrent clinical trial now, some other approach.

To frame that up, do you think it is just off the table permanently, whether it is a question that can be addressed by further research, and should that further research be commenced now or after accumulation of more data in the monotherapy situation, and potentially more evaluation of the subjects who were previously dosed, who have also been allowed to restart their treatment.

I would be interested in people's thoughts on that.

Dr. DeKosky.

DR. DeKOSKY: We heard yesterday that

there had been no cases of PML reported with the other medications, is that correct, up to this time, reported, although there may have been cases?

DR. KIEBURTZ: Sorry, there have been no cases reported?

DR. DeKOSKY: With the other drugs approved for long-term use in MS, is that correct?

DR. KIEBURTZ: I don't believe there has been any other reported cases of PML.

DR. DeKOSKY: So, my suggestion would be that I would go for (b), that if, in fact, this is largely about an interaction with this particular medication, that it would be useful to have some experience with this medication's ability to produce other cases before combining it, which was the circumstance, we think, under which it was unearthed.

So, I would wait. I wouldn't rule it out forever, but I would wait to see whether or not the signal was worse with longer experience with this drug. It is my opinion.

DR. KIEBURTZ: I think the confidence

interval around the current estimate, I mean the point estimate is 1 in 1,000, but that goes up to 3 in 1,000, and down to 1 in 10,000. I suppose any 99 percent confidence interval, 1 in 100 probably falls in there, so I think the more information you have might give you a sharper point estimate and narrow the confidence interval.

Is that--I am saying in a different way what I think I hear you saying.

DR. DeKOSKY: We are up to 5,000 cases being followed. That ought to narrow the confidence limits enough to let us make a realistic estimate of what the potential risks would be of doing another combination study.

DR. KIEBURTZ: Dr. Sacco and Dr. McArthur.

DR. SACCO: I think given our answer in No. 4, which was that we are not sure this could occur with use of this drug alone, that I would also agree with (b), that gaining more experience with continued use of the drug alone in a large sample, in probably more than 5,000. 5,000 will be in the cohort study, but in the registry, could be

even greater. We heard that in the first few months this drug became available, it was like 7,000 people were signing up to get it.

So, i would like to get that data before embarking on the next set of studies with combination therapy.

DR. McARTHUR: Is the question restricted to Avonex or, by implication, do you mean other approved agents in combination?

DR. WALTON: The question focused on Avonex because that happened to be the one concomitant use where we had some experience that natalizumab adds something, had benefit, but didn't have the efficacy data that other thing added to natalizumab offered additional benefit.

But it really does apply certainly to all the interferon-betas and really to any of the concomitant use drugs that might be thought of.

DR. McARTHUR: Then, I would go along with (b) .

DR. KIEBURTZ: Does anyone advocate (a) never evaluate concurrent use? Does anyone

advocate (c), which is permitting clinical trials of concurrent use of an approved medication with Tysabri--mind you this is research, clinical trials--right now, is anyone in favor of that?

MS. SITCOV: Could you please repeat that

DR. KIEBURTZ: Is anyone in favor of option (c), that is, initiating clinical trials at the time of re-approval of marketing?

[No response.]

DR. KIEBURTZ: I think we have uncharacteristic unanimity of opinion around option (b).

Dr. Temple.

DR. TEMPLE: Well, (c) is in the setting of a clinical trial, informed consent, and so on. Some of the points that people made earlier that we didn't really know how the drug works in people with aggressive primary progressive disease.

Do you think that couldn't even be studied in a combination form with informed people? That seems very strict.

DR. KIEBURTZ: Say the question again.

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DR. TEMPLE: Well, (c) is about whether, in an IND setting, you could look at concurrent use. So, what I am asking is if you took some aspect of MS that is not now well studied, people who aren't relapsing-remitting, but just going straight downhill, we don't really know what Tysabri does in that setting. That is a point that people have made repeatedly and yet that is a very difficult situation that you might think calls for risk taking.

So, under the setting of an IND, ordinarily, you think people are allowed to make those kinds of choices.

DR. KIEBURTZ: I think we might have been thinking about the circumstance only of the approved--I mean for relapsing-remitting, so maybe we should think about it a little more broadly.

Dr. DeKosky.

DR. DeKOSKY: I was wondering, Bob, if you meant that to be done in a combination therapy without, for example, doing the study of Tysabri first in primary progressive. I mean in terms of

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relative risk and the length of the consent form, I would at least like to know whether or not that drug worked.

DR. TEMPLE: You might even compare the combination with each of the singles in that setting.

DR. KIEBURTZ: So, you could have a factorial design, I think.

DR. TEMPLE: But really the point I am making is that we often, but not absolutely always if you are really scared, we often have more discretion in a setting of an investigational use where you can tell everybody, and they can say yes, I have waited, I have thought about it, I am willing. To say no would be a very unusual and strong statement about this. I just wondered if you really meant it.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I guess you were asking our advice. Obviously, the Agency will do what the Agency does, but I think first getting this information that we want to collect, that we are

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all concerned about first, I think is appropriate. I think first testing the drug as monotherapy in these other clinical situations is quite appropriate, and then if you get a signal on monotherapy, and this turns out to be relatively safe as monotherapy, then, if you want to go ahead and then look at combinations, I think that is an entirely reasonable approach.

We are concerned about this. That is what this whole discussion has been about.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I completely agree in the sense that I think it is fair to do it under an investigational status, and I definitely think that monotherapy needs to be tried first. There is very few other things that have shown efficacy actually in the progressive varieties.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I think just a point earlier of the same thing, with progressive MS, I think we should do monotherapy. I was concerned the drug was going to get used in all of these other MS

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varieties, as well, so I would very much say let's do other trials for other kinds of MS, but probably stick with monotherapy or direct head-to-head comparisons of two single active drugs.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: The same as Dr. Goldstein, but just restating it. I think we need to allow the system, the registry, the drug distribution, collection of information from the pre-infusion, I think we need to allow that system to show that it can work either just in terms of the logistics of collecting the data. Hopefully, we are not going to see any signal in terms of PML cases, but just to show that the system itself can work.

DR. KIEBURTZ: I would be interested if committee members are comfortable in trying to quantify what would be adequate additional monotherapy observation, like how many thousands of person years additional, you know, another 5,000, another 10,000, because if we say we would like to get some more, are we able to quantify how much more before it's enough?

DR. McARTHUR: If there were 7,000 patients who enrolled within the first few months, I think to get 5,000 times two years, that is 10,000 patient years would be a pretty reasonable number.

DR. KIEBURTZ: My guess is they would be able to accumulate 10,000 person years of experience in less than two years, my guess.

Dr. Goldstein.

DR. GOLDSTEIN: There is a corollary to that question, and it was one that was raised yesterday, is we are doing all of this surveillance and we are looking for these adverse events. What level of adverse events would trigger concern, one case, two cases, 10 cases? Where is the trigger going to be pulled? Do we have any feeling for that?

DR. KIEBURTZ: I am not sure.

DR. WALTON: I think if we see cases that raise our concern again, it is entirely possible that we will be inviting you back to discuss this again. That, after all, is what triggered this

advisory committee in the first place, the occurrence of these cases.

DR. KIEBURTZ: I think we made our decision-making around the notion that the point estimate of 1 in 1,000 is about right, and that if accumulated experience starts to move that point estimate upwards significantly, I think it would be reasonable to reevaluate this discussion. What does upward significantly mean? I don't know, but we will know it when we see it.

DR. TEMPLE: As Russ said when we started, we expect cases, and if they are at about that rate, we would hardly be surprised. We don't necessarily believe that it is only because of concomitant therapy that these cases occurred. For all we know, it is going to be exactly the same with monotherapy. That is our ongoing assumption even though we don't want anybody to do anything but use monotherapy, we don't really know.

DR. KIEBURTZ: I think the committee members, I hope have deliberated in awareness that it is likely that there will be cases of PML, and

it is likely that there will be deaths from it. I mean that has to be the background against which we are making these decisions.

The point is that there is death and disability associated with other interventions that are approved and on the market, and against the face of the disability and death that occurs with the illness, is it a reasonable balance that an informed physician and patient, clinician and patient can make together, and I think our unanimous decision was that was yes with certain restrictions.

That may need to be revisited based on the actual observed frequency of the problem with more people, over a longer period of time.

Dr. McArthur.

DR. McARTHUR: So, if in the unhappy event that a patient on monotherapy does develop PML, should we have a developed plan of exactly what to do, what to tell that patient? I realize there are no proven therapies for PML, but there are some, let's just call them alternative therapies that are

being proposed.

Certainly in the HIV literature, at least one of the patients in our packet received several forms of antivirals. Do we have an emergency plan is what I am asking.

DR. KATZ: I don't think one specific plan has been proposed, and I am not sure we are in a position at this point to say what one should do in a case of a case. Clearly, that will have to be thought about, but I am not sure, I am not an expert clearly, and I don't know that there is a treatment algorithm for patients who get PML.

I am sure, as you say, there are multiple different sorts of treatments that people give. I don't think we are in a position to mandate a particular one at this point.

DR. McARTHUR: I am looking at you, but maybe I should be asking the sponsor what is the emergency plan for if and when a patient on Tysabri monotherapy gets PML. What will happen?

DR. KIEBURTZ: Dr. Sandrock or does anyone--I mean you don't have to reply to that, but

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if you are interested--sorry, that's a little loose. I mean if you are willing to share your thoughts on it now.

DR. SANDROCK: Our recommendation is obviously to suspend natalizumab. We are talking to some of the investigators about the possibility of using plasma exchange as a way of removing natalizumab more quickly, but that is just one of our thoughts.

DR. KIEBURTZ: The other part of Dr. McArthur's question, is there any specific clinical management of PML should it happen beyond trying to remove the agent, any antiviral treatment plan or other treatment plan that has been articulated? It is perfectly acceptable to say you are thinking about it.

DR. CLIFFORD: Well, clearly, there is no correct answer that has been demonstrated for the treatment of PML. Only two years ago I was standing in an international meeting proposing interferon-beta as an excellent plan for a controlled trial of treatment for PML in HIV

patients, and I think that I have given up on that as a primary hypothesis, but the flip side of that is that I am not at all--with the Agency--I am not at all convinced that interferon has anything to do with incidental happening that both of the cases that were observed in MS were in interferon-treated patients. I think that that is something that could have very easily happened by chance.

On a theoretical basis, the interferons have activity against DNA viruses. We have used interferon-alpha. Quite recently, several of us have published on a number of cases where we have actively thought that there might be a signal of activity of interferons against JC virus, so that has actually been on the table fairly recently.

In terms of the theoretical approach, the use of cytosine arabinoside has the best in vitro evidence, and while my group did a control trial that did not demonstrate in the pre-HAART era that this was an effective treatment for PML, we have revisited the thought, because we really believe the problem is drug penetration, and it is very

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possible that in the setting what we will see--if we see another case associated with natalizumab, it is very possible that there will be an inflammatory reaction, that there will be more breakdown of the blood-brain barrier as the drug is withdrawn, and the JC infection is exposed to an increasingly active immune response, and that we could augment that with cytosine arabinoside.

So, I think that is something that I would actively consider, but all of these things are really investigational approaches, and we could certainly have discussions about giving a formula, but it would turn into another trial, and I hope there will not be enough patients to really do a meaningful trial. If there were, then, I suspect we would be stopping again anyway.

DR. KIEBURTZ: Thank you, Dr. Clifford.

Dr. Sacco.

DR. SACCO: I just wanted to check. I know we are getting to the end of the questions, if there may be another, but we never touched on, and I thought you were going to bring it up, the issue

of neutralizing antibodies and whether that has a role in any of our deliberations.

I thought it was in our questions, and I am realizing, we got to the end now, and it hasn't been unless there is a new question we don't know about.

DR. KIEBURTZ: It does go back to what would be--8(h), should there be some routine testing for neutralizing antibodies, or should that be in response to some clinical event, because the presence of neutralizing antibodies seems to be a signal for increased risk and decreased efficacy, so the risk-benefit ratio would be perturbed.

The question is should testing only be driven by clinical events, or should it be done at some specified time points as a mandatory part of use.

Thoughts on that?

DR. KOSKI: Certainly patients who had maybe infusion reactions early on, patients that appeared to have progression in their symptoms. Their MRI did not show something that might be

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compatible with PML. I mean you would want to look and see if these antibodies are there since it is associated with decreased efficiency, and also infusion reactions.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I don't know how this works with the FDA and the sponsor, but I mean whether there would be a recommendation to check antibodies should symptoms occur, and then consider discontinuation of the medicine?

DR. KIEBURTZ: A recommendation is certainly something that could be proposed. The question is would it be required, and the discussion I hear is mostly--I mean if it was required, everyone would have it done at a certain time point no matter what their symptoms were.

I don't hear a lot of enthusiasm for that, but it could be required or strongly recommended in the setting of certain clinical phenomena including lack of clinical benefit and the occurrence of certain kinds of adverse events.

DR. DeKOSKY: I am remembering that the

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development of the antibodies was relatively early in the course, that if you didn't have them by 12 weeks, you probably weren't going to get them, so we might want to temper that. Someone that is having response problems a year out, that that may not be a terribly useful thing to go after.

The other thing we didn't discuss, and I am not sure if you need feedback about it or not, is frequency of high-dose methylprednisolone for breakthroughs. We didn't discuss that and whether at some frequency, reconstitute immunosuppression or immunomodulation.

DR. KIEBURTZ: And hence, whether the drug should be restricted if you are having a certain frequency? I think these things are going to intersect because if you are having a high rate of relapse, you are going to get imaged again, these other things are going to happen, so that it will probably be driven by those clinical events is my guess. It is not going to pan out that someone is going to have a high exposure to pulse steroids, and not be getting these other things happening.

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Is that fair?

DR. McARTHUR: That's fair.

DR. KIEBURTZ: I detect a certain group fatigue, but we will persevere if there is other important issues that the Agency would like us to address.

DR. McARTHUR: Dr. Kieburtz, I just found another page of questions here.

[Laughter.]

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I think you have answered our questions. I would like very much to thank the committee. It has been very difficult and I think you have managed to get through the questions and give us all the information we need. So, I very much appreciate your doing that.

I would also just like to acknowledge the folks who spoke in the public session, who were particularly courageous, not only handling their illness or their family members' illness, but coming here and giving their testimony. That is a difficult thing to do.

Finally, last but not least, I would really like to publicly acknowledge the Agency's presenters. You saw the slide of all the people who were involved in looking at these data, and there were probably even more than that, but the folks who presented - Alice Hughes, Susan McDermott, Diane Wysowski did a tremendous amount of work in a very, very short period of time, and their presentations were only the tip of the iceberg of the amount of work that they actually put in, and I think they need to be acknowledged.

Also, two folks who didn't speak here today, who have done a tremendous amount of work preparing for this, Wilson Bryan and Kathy Needleman in the Division, so I would really like to acknowledge their efforts. I think it has been extraordinary.

DR. KIEBURTZ: Could I just say I have had several discussion with the committee members, and I just want to reiterate some of those comments. First of all, I know it is very difficult for the sponsor to have so many things they would like to

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say, and we don't call on you in the circumstance, and I am sure you are familiar with that, but thank you for the comments you did provide and the information you provided, which was very helpful and effectively organized, and for answering our questions when we had them.

And to the FDA for presenting very clearly and providing us materials that were cogently organized and obviously reflect a lot of work, and just to reiterate, the open public hearing was particularly--of course, it was moving, but it was also instructive, and as many of you might realize, it is an incredibly courageous thing to get up and say those things in public, particularly when they have such an emotional content, so we thank those speakers for their willingness and courageousness in doing that.

I would just like to thank the members of the committee for sticking with it, these are tricky issues, for the Agency for having forbearance with us in not necessarily given concise answers in open discussion.

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Unless there is anything else that needs to be said, I think I will adjourn the meeting at this time.

[Whereupon, at 3:15 p.m., the proceedings were adjourned.]

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